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PENICILLIN TREATMENT OF ERB'S SYPHILITIC SPINAL SPASTIC PARAPLEGIA

Report of Four Cases, One with Autopsy[1]

HAROLD A. TUCKER, M.D.

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INTRODUCTION

The evaluation of penicillin as an agent in the treatment of neurosyphilis is still in its early stages, although all the more usual types have been treated (1–6). One of the less common, although by no means rare, manifestations of this disease is the syphilitic spinal spastic paraplegia described by Erb (7). The outstanding feature of this condition is spasticity of the lower extremities, usually symmetrical in distribution and progressive in character. Ankle clonus, increased deep tendon reflexes and diminished superficial ones are often found. Disturbances of micturition may be present. As a rule, mental status and sensory responses remain within the limits of normal. Peters (8) has recently shown that the majority of these patients have positive blood and spinal fluid reactions for syphilis. Treatment has been eminently unsatisfactory by all previously employed methods. The disease usually progresses with variable rapidity to complete paralysis of the lower extremities and even death due to intercurrent infection (9, 10).

The absence of published information as to the effect of penicillin therapy in this type of neurosyphilis has made this study one of an essentially experimental nature; total dosages and schedules of administration were selected arbitrarily at first, altered as experience grew. These factors, together with the interesting clinical features in these patients, make it worthwhile reporting them in some detail; in one case autopsy data are appended.

REPORT OF CASES

Case 1 (J. H. H. 325981). A sixty-five year old white merchant was first admitted to The Johns Hopkins Hospital on July 7, 1944, complaining of stiff,

[1] The work in this paper was done under a contract recommended by The Committee on Medical Research, between the Office of Scientific Research and Development and The Johns Hopkins University.

The photomicrographs were taken by Phillip C. Pratt, M.D

"cold" legs and difficulty in walking of two years' duration and of hesitancy of micturition for several months. About 1904 he had had a chancre treated with local applications of mercury ointment for six weeks. With the onset of the affliction of his lower extremities, he had consulted a physician who found positive blood and spinal fluid tests for syphilis and gave him eight weekly intramuscular and intravenous injections. A year later, symptoms persisting, arsenic and bismuth treatment had been administered for six weeks more. Shortly thereafter he had noted increased trouble in starting the stream of urine, nocturia, and occasional nocturnal dribbling.

On admission, the gait was distinctly spastic. Other pertinent physical abnormalities were absent abdominal reflexes, increased knee and ankle reflexes, a bilaterally positive Babinski sign, and bilateral ankle clonus. A neurologic consultant said the picture was that of a selective, slowly progressive pyramidal tract involvement identical with Erb's spastic paraplegia.

The patient was given 2,000,000 Oxford units of sodium penicillin in aqueous solution in intramuscular injections of 25,000 units each every three hours for ten days. A severe pyuria, and later, urinary retention complicated his course in the hospital. Urologic study disclosed a hyperplastic prostate gland. Following transurethral resection (Dr. J. A. C. Colston), the patient experienced much relief from urinary tract symptoms and he was discharged from the ward improved on August 4.

When next seen in November, 1944, he felt he had been benefited, estimating his own improvement at 10 per cent. Laboratory data (table 1) did not bear this out, however, and it was found for the first time that the vibratory sense in the legs was absent.

Reexamination four months later gave objective evidence of progression; the patient also felt this to be true and it was decided that more treatment was indicated. He was readmitted to the ward on March 8, 1945, 242 days after his first course of penicillin, and was given 1,760,000 Oxford units of sodium penicillin intramuscularly, 40,000 units every three hours for forty-four injections. As with the former course, no Herxheimer reaction occurred and he was discharged, clinically unchanged, on March 23.

This patient lives at a considerable distance from Baltimore. On July 20, 1945, 376 days after receiving his first penicillin, he wrote that he did not believe the antibiotic agent had done him any good. "It seems to me the case has advanced . . . . . ."

Case 2 (J. H. H. 242510). A thirty-six year old white merchant was first admitted to The Johns Hopkins Hospital for the malarial therapy of late neurosyphilis on September 29, 1941. There was a history of a chancre in 1925 treated with six or eight injections of "606." There were no further symptoms until 1939, when he began to have some difficulty in walking. One private physician

gave him six or eight more injections of "606," then referred him to a second who continued intravenous and intramuscular injections for about one year.

Physical examination on entry to the hospital yielded the following pertinent data: pronounced spasticity of both legs, ankle clonus, extensor plantar responses,

TABLE 1

The course under penicillin therapy of case 1

DATE	DAYS AFTER START OF PENICILLIN	TREATMENT RECEIVED	BLOOD STS*	SPINAL FLUID				REMARKS
				Cells	Prot.	WaR†	Mastic	
1904		Mercury ointment						Primary syphilis
1942		8 Arsenic 8 Bismuth						
1943		6 Arsenic 6 Bismuth						
7/ 7/44				1	88	pos. with 0.03 cc.	4554310000	
7/10/44	0–11	Penicillin, 2,000,000 units						*First admission*
7/21/44	12							Transurethral resection
7/29/44	20		2	0	83	pos. with 0.03 cc.	4555543210	
11/14/44	128		2	3	50	pos. with 0.05 cc.	5544321000	Progression
3/ 8/45	242 (0–6)	Penicillin, 1,760,000 units	2	6	78	pos. with 0.03 cc.	4432100000	*Second admission*
7/20/45	376 (135)							Getting steadily worse (letter)

* Serologic test for syphilis, in Eagle units.

† Wassermann reaction.

and a hyperacute deep pain sense. No symptoms referable to the bladder had been noted. It was thought most of the damage to the spinal cord was limited to the pyramidal tracts. Laboratory data on this patient are summarized in table 2.

The patient was given an intravenous injection of eight cubic centimeters of blood from a patient with tertian malaria and five days later rigors began.

TABLE 2

The course under penicillin therapy of case 2

DATE	DAYS AFTER START OF PENICILLIN	TREATMENT RECEIVED	BLOOD STS	SPINAL FLUID				REMARKS
				Cells	Prot.	WaR	Mastic	
1925		6–8 "606"						Primary syphilis
1939		6–8 "606"						
1940–41		"IV" and "IM" injections, 1 yr.						
9/29/41		Malaria; 3 Mapharsen	0	3	40	pos. with 0.6 cc.	5554333222	*First admission*; had 11 rigors, 53.5 hrs. over 40°C.
4/29/42		52 Trypars-amide 12 Bismuth	0	0	37	pos. with 0.6 cc.	4321000000	
11/20/42			0	0	25	pos. with 0.8 cc.	5554100000	
6/ 4/43			0	15	25	pos. with 0.6 cc.	5555431000	Spasticity increasing
3/ 1/44			0	9	56	pos. with 0.6 cc.	4443210000	
3/23/44	0–11	Penicillin, 4,000,000 units	0					*Second admission*
4/ 3/44	12			145	44	Anticomplementary	5553100000	
8/25/44	156		0	2	40	pos. with 0.8 cc.	5554210000	Status unchanged
6/26/45	461							Getting steadily worse (letter)
7/24/45	489 (0–9)	Penicillin, 2,560,000 units						
10/25/45	582 (94)		0	5	37	Dbt. with 0.8 cc.	5422111000	*Third admission.* Spasticity increased

He had eleven malarial paroxysms with a total of 53.5 hours of rectal temperature elevation over 40°C. (104°F.). He was then discharged from the ward as improved. During the ensuing year his private physician gave him fifty-two weekly injections of tryparsamide (3.0 grams) and twelve weekly injections of bismuth subsalicylate in oil (0.2 gram). Subsequent to the malarial treatment there was almost complete loss of libido and potentia, but there were no disturbances of bladder function.

In June, 1943, it had become necessary for him to use a cane occasionally in order to get about comfortably, but objective evidence of progression was slight. By March 23, 1944, he had to use a cane at all times. The previously noted neurologic abnormalities were still present; spasticity of the legs had increased and no superficial abdominal reflexes could be obtained. Although the outlook was grave in view of the many types of treatment previously employed, an experimental trial of penicillin therapy was considered advisable. He was readmitted to the ward and given 50,000 Oxford units of sodium penicillin in aqueous solution intramuscularly every three hours for a total of eighty injections, 4,000,000 units in ten days. There was no Herxheimer reaction. No improvement in his condition was apparent when he was discharged April 4, 1944.

The patient was next seen August 25, 1944; he believed his condition to be worse, but objectively his status was essentially as it had been prior to treatment. He now sought help elsewhere. One physician gave him six intrathecal injections of pyridoxine (dosage unknown). Following the first dose some symptomatic relief, probably psychologic, was noted for one or two days; subsequent injections produced no similar results. He was next given 2,560,000 Oxford units of sodium penicillin in eight days at another hospital, 40,000 units being injected intramuscularly every three hours for sixty-four injections. Because libido and potentia were now greatly diminished or absent, still another physician administered seven weekly injections of mapharsen and testosterone proprionate (both said by the patient to have been given by the intramuscular route) without noticeable effect.

On October 25, 1945, 582 days after the start of his original penicillin treatment, the most recent exhaustive examination was carried out. His condition had unquestionably grown worse. Walking was possible only with a cane and for short distances; he had become unable to walk the 200 yards from his home to his office. Spasticity was more pronounced, even light percussion over the appropriate tendons producing sustained clonus. Superficial abdominal reflexes were absent; cremasteric reflexes were hypoactive. Potentia and libido were lost, but all modalities of sensation were unimpaired. Progression of the disease had occurred in spite of the various types of therapy administered.

Case 3 (J. H. H. 327581). A thirty-seven year old Negro laborer was first seen in the Out-Patient Clinic of The Johns Hopkins Hospital July 12, 1944, because of stiffness in the legs of five weeks' duration and of constipation and difficulty starting the urinary stream for two weeks. He had had a penile lesion and positive blood serologic tests for syphilis in 1929, and had been inadequately

treated elsewhere. In 1936 a blood test was said to have been negative. When examined in the clinic the gait was spastic. Hyperactive knee and ankle reflexes were present; ankle clonus and extensor plantar responses were obtained bilaterally. Faint upper but no lower abdominal or cremasteric reflexes could be elicited. All modalities of sensation were normal. The urinary bladder was enlarged to within four centimeters of the umbilicus and anal sphincter tone was increased. These observations, together with laboratory studies (table 3), resulted in his admission to the ward on July 25 for penicillin treatment of syphilitic spinal spastic paraplegia.

During his first hospital admission the patient received 50,000 Oxford units of sodium penicillin in aqueous solution intramuscularly every three hours for eighty injections, a total of 4,000,000 units in ten days. Cystometry disclosed an "atonic" bladder with normal vesical sensation; even when he strained, the intravesical pressure did not rise above 35 millimeters of mercury. He was afebrile throughout and was discharged from the hospital on August 5 slightly improved.

Since subsequent examinations revealed steady progression of symptoms, he was readmitted to the ward on October 23, 1944, and the original schedule of penicillin treatment was repeated. As before, no Herxheimer reaction was noted. Several areas of ulceration which had appeared in the skin of the low back responded to this therapy, but a severe pyuria complicated the picture and he was discharged unimproved on November 3.

The patient was now bedridden at home; his decubitus ulcers broke down rapidly and twenty-five days later hospitalization again became necessary. He had become somewhat undernourished in appearance, had large infected skin lesions in the sacral region and the spasticity of the lower extremities had increased. Except for the absence of pain in the ulcerations, sensation remained unimpaired. Lumbar puncture gave no evidence of subarachnoid block. Sulfadiazine (21.0 grams in eleven days) greatly modified the urinary tract infection (*Proteus morgagni* and *β-streptococci*, Lancefield Group D), but it was apparent that previous types of treatment had not arrested the underlying process. Drastic therapeutic measures appeared to be indicated, and he was inoculated intravenously with eight cubic centimeters of blood from a patient with quartan malaria and discharged from the ward to await the onset of fever.

Eleven days later, nocturnal chills and fever developed and the patient returned for his final hospital admission on December 22, 1944. The ulcers had increased in extent and depth; anemia and cachexia were profound. Although he had a sustained temperature elevation, no malarial parasites were ever seen in the peripheral blood and a leukocytosis varying from 20,900 to 30,450 leukocytes per cubic millimeter of blood was reported. It was doubted whether clinical malaria was present, the clinical manifestations being explained on the basis of sepsis secondary to the ulcerations and to the infection of the urinary tract. One week after admission *Clostridium welchii* was identified by culture of material from the skin lesions. Surgical intervention and the administration of sulfamerazine (135.0 grams in forty-three days) were unavailing; the course was steadily

TABLE 3

The course under penicillin therapy of case 3

DATE	DAYS AFTER START OF PENICILLIN	TREATMENT RECEIVED	BLOOD STS	SPINAL FLUID				REMARKS
				Cells	Prot.	WaR	Mastic	
1929–30		15 Arsenic 7 Bismuth						Primary syphilis (?)
7/25/44	0–11	Penicillin, 4,000,000 units	0	35	51	pos. with 0.03 cc.	5554321000	*First admission*
8/ 5/44	12		2	25	51	pos. with 0.05 cc.	5555443300	
9/ 7/44	45		2					Steady loss of motor power; increased urinary difficulties
10/ 5/44	73		1					
10/12/44	80			9	40	pos. with 0.05 cc.	5554300000	Skin ulcers developing
10/23/44	91 (0–11)	Penicillin, 4,000,000 units	0					*Second admission;* complete incontinence, paraplegia
11/ 2/44	101 (11)			9	37	pos. with 0.05 cc.	5543210000	
11/28/44	127 (37)		1	5	37	pos. with 0.1 cc.	5544330000	
12/ 1/44	130 (40)	Sulfadiazine						*Third admission;* inoc. quartan malaria
12/21/44	150 (60)	Malarial rigors (?)						*Final admission*
12/26/44	155 (65)	Sulfamerazine						
12/29/44	158 (68)							*Cl. welchii* cultured from ulcers; fever, progressive cachexia
2/ 8/45	199 (109)							Death

downhill and he expired on February 8, 1945, 199 days after receiving his first injection of penicillin.

The *autopsy*, performed 10.5 hours after death, disclosed deep decubitus ulcers over the hips and sacrum measuring from 14 to 21 centimeters in diameter. From these *Clostridium welchii* was obtained by culture. Over the vertebral spinous processes and the lower extremities there were numerous smaller ulcers. On gross examination the heart and aorta were essentially normal as were the kidneys. The bladder wall was contracted, thick, and lined with dusky red

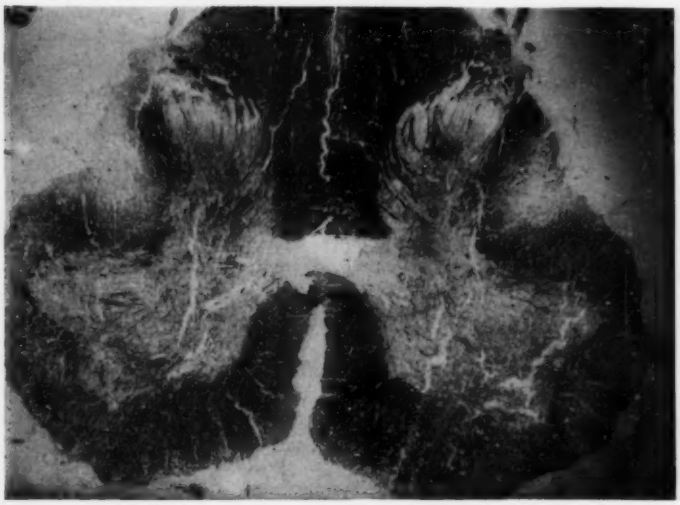

FIG. 1. SECTION THROUGH LUMBAR SPINAL CORD ILLUSTRATING DISTINCT DEGENERATION OF MYELIN SHEATHS IN THE AREAS OCCUPIED BY THE CORTICOSPINAL TRACTS (MYELIN SHEATH STAIN)

mucosa. Two prostatic abscesses, each measuring 1.5 centimeters in diameter, were seen. The spleen was within the limits of normal as to size, shape, and consistency.

The leptomeninges were uniform and delicate and cerebral configuration appeared normal. The brain and the entire spinal cord, together with its enveloping membranes, were removed. Neither meninges nor blood vessels were unusual but the regions of the spinal cord occupied by the anterolateral columns were translucent as compared to the posterior portions.

Microscopic studies of the aorta yielded no evidence of syphilis. Distinct chronic cystitis and prostatitis were seen, however, as were the periurethral ab-

scesses. Neither malarial parasites nor pigment were observed in the brain, spleen, liver, or bone marrow.

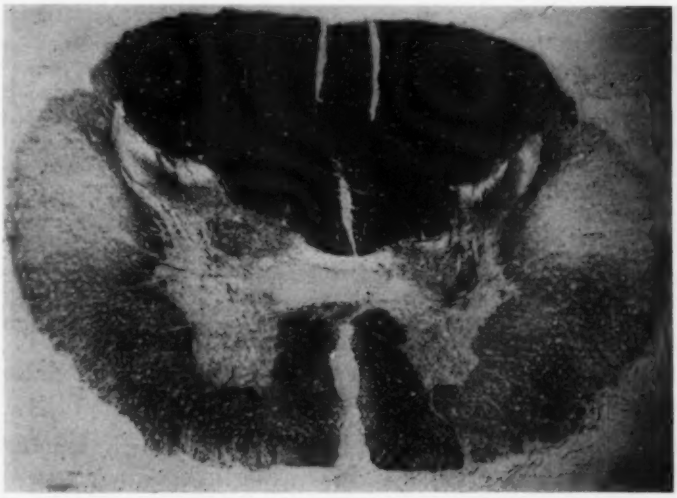

FIG. 2. SECTION THROUGH LOWER THORACIC SPINAL CORD SHOWING PRESERVATION OF POSTERIOR COLUMNS AS COMPARED TO THE ANTEROLATERAL PORTIONS AND PROFOUND PYRAMIDAL TRACT DEMYELINIZATION (MYELIN SHEATH STAIN)

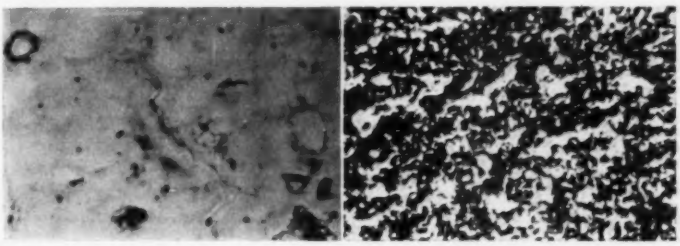

FIG. 3a FIG. 3b

FIG. 3. In myelin sheath preparations under higher magnification (× 200) extensive degeneration is seen in the corticospinal tracts (figure 3 A) as compared to the posterior columns (figure 3 B).

Sections of the central nervous system were prepared for study with a modified Spielmeyer's myelin sheath stain. In preparations taken from the lumbar and lower thoracic regions of the spinal cord (figures 1–3) degeneration of myelin

sheaths was apparent in all the descending tracts, especially the corticospinal tracts. Stains for fat (Sudan IV) demonstrated a moderately diffuse accumulation of fat in the regions of myelin degeneration in the anterolateral portions of the spinal cord. The posterior columns contained well preserved myelin sheaths (figure 3B) and the anterior horn cells appeared to be of normal size, shape, and number in the preparations examined. A section of the medulla oblongata illustrated degeneration of the ventral spinocerebellar tracts and possibly the lateral spinothalamic tracts, but the medial lemniscus was preserved. The myelin sheaths seemed intact or only slightly altered in the corticospinal tracts at this level although stains for fat demonstrated small globules of fat scattered throughout these tracts on both sides. A section of the cerebellum contained some small foci of rarefaction in the white matter which suggested focal degeneration, but myelin sheath stains did not bear this out. No definite lesions were found in the portions of cerebrum studied. A few lymphocytes were seen in the meninges but no significant vascular alterations were apparent.

The final anatomic diagnoses were: Neurosyphilis, late, of spinal cord, with anterolateral degeneration, most complete in the corticospinal tracts below the medulla oblongata; decubitus ulcers (*Clostridium welchii*); chronic cystitis and prostatitis with abscess formation; malaria inoculata (history).

Comment. The observations in this case are entirely compatible with the diagnosis of Erb's syphilitic spinal spastic paraplegia. Although the course of the disease is usually chronic with a tendency to remission, and even to complete arrest in some cases, the total duration of symptoms in this patient was less than nine months. That such a course may occur in spinal cord syphilitic processes is not necessarily remarkable when it is borne in mind that cerebral involvement (paresis) also tends to be chronic but in certain instances progresses with startling rapidity in spite of all forms of treatment. Once symptoms appear, it is sometimes observed according to Winkelman (11) that "death takes place in a comparatively short time, the result either of bladder infection which ascends to the kidneys or of extensive bed sores with toxemia." Renal involvement was minimal or absent in this patient and the immediate cause of death was probably the clostridial infection of the decubitus ulcers.

No clinical evidence of motor involvement in any area other than the pyramidal tracts was seen at any time, nor could symptoms of ataxia be demonstrated in this patient. In view of the diffuse anterolateral myelin degeneration of the lower portion of the spinal cord, it is suggested that the absence of such clinical evidence may have been more

apparent than real. The presence of extreme spasticity in the involved extremities may have precluded evaluation of the other less obvious

TABLE 4

The course under penicillin therapy of case 4

DATE	DAYS AFTER START OF PENICILLIN	TREATMENT RECEIVED	BLOOD STS	SPINAL FLUID				REMARKS
				Cells	Prot.	WaR	Mastic	
1916		6 Salvarsan						Primary syphilis (?)
7/16/45			16	36	123	pos. with 0.03 cc.	5554310000	*First admission*
7/17/45								Tonsillectomy and adenoidectomy
7/19/45								Inoculated with tertian malaria
7/23/45		Malarial rigors						Had 11 rigors with 64 hrs. fever over 40°C.
	0–26	Penicillin, 10,000,000 units						
7/26/45	4		16					
8/ 3/45	12		32	48	58	pos. with 0.05 cc.	1222000000	
8/17/45	26		32	19	74	pos. with 0.1 cc.	2344320000	
8/25/45	34							Gait more spastic than prior to treatment
10/17/45	87		64					Status unchanged
11/20/45	121		64	9	57	pos. with 0.05 cc.	1111100000	*Second admission;* status essentially unchanged

motor functions. It is also significant that degeneration of the descending tracts, as noted in sections of the spinal cord at various levels, was extreme in the lower thoracic region whereas only slight myelin degen-

eration, evidenced by scattered globules of fat, was found in the corresponding areas of the medulla oblongata. In spite of the extensive pathologic alterations seen, the only sensory impairment noted was lack of pain in the decubitus ulcers.

Case 4 (J. H. H. 357354). A fifty-three year old white shipyard worker was referred by an otolaryngologist because of a routine positive serologic blood test for syphilis. Although his chief presenting complaint had been of sore throat, it developed that he had noted stiffness and crampiness in the legs for over a year and slight difficulty starting the urinary stream promptly for about two weeks. A penile lesion in 1916 had been treated with a total of only six injections of salvarsan. Several subsequent serologic blood tests for syphilis were said to have been negative and significant skin lesions were denied. Physical examination disclosed the following pertinent data: although the gait was slightly spastic in character after resting, it improved rapidly during exercise; increased deep and diminished superficial reflexes, extensor plantar responses and bilateral ankle clonus were noted; there was a papilloma on the right tonsil.

He was admitted to The Johns Hopkins Hospital on July 16, 1945, and inoculated intravenously with eight cubic centimeters of blood from a patient with tertian malaria; tonsillectomy and adenoidectomy (Dr. Arthur Ward) were performed the following morning. Seven days later rigors began and with their onset 50,000 Oxford units of sodium penicillin in aqueous solution were injected intramuscularly every three hours for twenty-five days, a total of 10,000,000 units in 200 doses. He had eleven malarial paroxysms with a total of sixty-four hours of rectal temperature elevation over 40°C. (104°F.). Serologic reports are listed in table 4. Cystometric studies (figure 4) nicely demonstrated the combination of normal vesical sensation and impaired motor innervation (12). Following treatment his gait was distinctly more spastic and he was discharged from the ward unimproved.

This patient was reexamined eighty-seven days later. Although he no longer had nocturnal cramps in his legs, spasticity had not lessened since leaving the hospital. Urinary hesitancy of about the same degree was still a complaint. Sexual desire and capacity had been normal prior to treatment, but now potentia was greatly decreased. Although he felt he had been generally benefited, objectively he was worse than he had been before treatment.

On November 20, 121 days from the start of therapy, this patient was readmitted to the ward for evaluation. He stated his gait was now definitely more spastic than before treatment; worse in the morning, it improved somewhat during the day. Although he could walk uphill without concern he had noted a tendency to progressive acceleration and falling when going downhill. Urinary complaints were as before and potentia was essentially absent. On physical examination his status was not significantly different; hypertonia of the lower extremities had not increased. From the laboratory standpoint, both blood and spinal fluid tests for syphilis remained strongly positive. Cystometry, performed by the same oper-

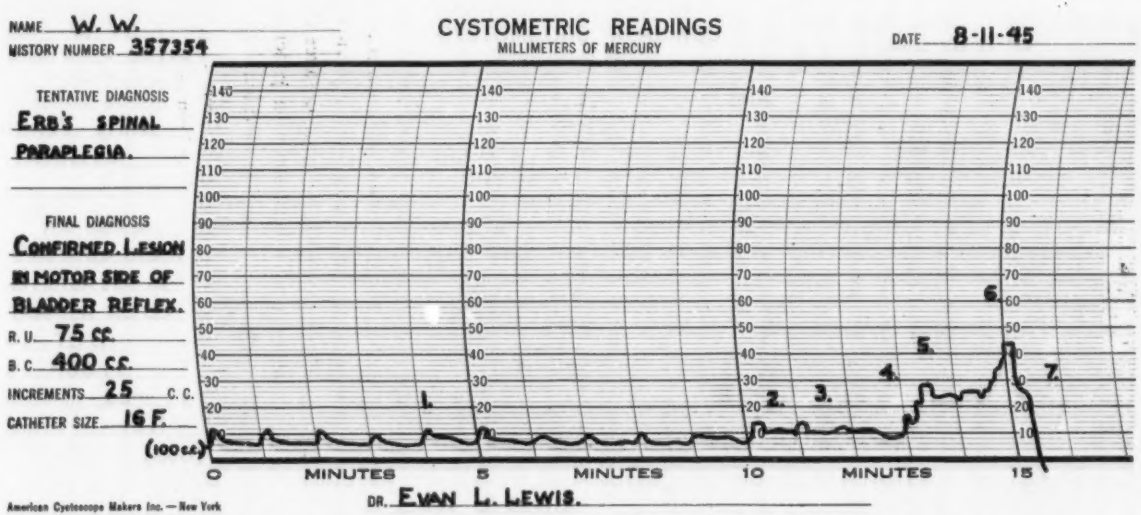

FIG. 4 (CASE 4). TYPICAL CYSTOMETROGRAM IN ERB'S SYPHILITIC SPINAL SPASTIC PARAPLEGIA

Normal "first desire" (1) was felt when bladder contained 225 cc.; at 400 cc. (2) "intense desire" occurred (normal); release of inhibitions (3) permitted initiation of bladder reflex which did not produce any measurable effect for 1.5 minutes (4). Maximum bladder contraction to an intravesicular pressure of 28 mm. of mercury (5) was insufficient to start urinary stream. By means of voluntary straining (6) pressure was raised to 43 mm. of mercury and voiding began (7). The tracing illustrates normal afferent impulse-transmission but a pathologic efferent response both in regard to time required for impulse-transmission and effective strength of vesicular contraction.

ator, was suggestive of some improvement in that no residual urine was present, the voiding reflex was said to be of better quality and bladder tonicity had increased since the previous examination. The final consensus, however, was that his status had not materially changed since discharge from the hospital at the termination of the combined penicillin-fever treatment.

DISCUSSION

Erb's syphilitic spinal spastic paraplegia has long been associated with demonstrable pathologic alterations in the spinal cord. This study was essentially one of an experimental nature to determine whether or not the clinical progress of the disease could be arrested by the administration of the antibiotic agent penicillin; restitution of destroyed nervous tissue was not to have been expected. In the light of past experience with other methods of treatment, encouraging results were not anticipated. Both clinical and laboratory studies were carried out with frequency and detail, however, in an effort to appraise fairly the effect of penicillin in this disease.

In the patients reported, infection with syphilis was of long duration, the period from the chancre until the onset of spinal cord symptoms being roughly 38, 14, 15, and 28 years respectively. Grossly inadequate treatment had been administered to each at the time of the original lesion. In only one patient (Case 2) did arsenic and bismuth therapy approach the amount suggested by present standards, but it was given after symptoms of central nervous system involvement had appeared.

The amounts of penicillin initially employed ranged from 2,000,000 to 10,000,000 Oxford units*; in three instances a second course was administered. In all cases the intramuscular route was used, injections being given every three hours day and night. The total dosages of penicillin were selected on an experimental basis only. In general, the earlier patients received the smaller amounts. As evidence ap-

* Vials of dried commercial penicillin from different manufacturers and at different times which were labelled "100,000 Oxford units" have been found actually to contain from approximately 85 to 200 per cent of that amount (14). No specific information is available as to the absolute total amounts of penicillin administered to the patients here reported but it is evident that individual courses of treatment varied between a minimum of 1,700,000 and a maximum of 20,000,000 Oxford units.

peared indicating that a dosage of 2,000,000 units was not effective, larger quantities were administered; the most recently treated patient (Case 4) was given 10,000,000 units together with malarial fever therapy. Intrathecal injections were not deemed advisable (5, 6, 13).

In the light of recent work on some fractions or derivatives of commercial penicillins, e.g. penicillins F, G, X, K, and others less widely publicized, it has become apparent that demonstrable differences in specificity and activity occur. From the evidence at hand, the patients here reported received mixtures containing G, F and K in unknown proportions. Those treated early in the study probably received penicillin G in larger amounts whereas the proportion of penicillin K was increased in products administered since mid-1944. Little or no penicillin X was present due to the almost universal use of chloroform-extraction in the manufacturing processes (14). Should subsequent work show that different fractions produce significant differences in response in patients with neurosyphilis, it may later be necessary to modify to some extent opinions expressed in the following discussion.

Results of treatment in this condition have been consistently disappointing in the past (9–11, 15), the process characteristically progressing in spite of all older methods of antisyphilitic therapy. The lists of therapeutic measures tested on these reported patients illustrate well this assertion (tables 1–4). The cases reported here have been followed from 121 to 582 days after the start of penicillin therapy without substantial clinical evidence of arrest or improvement of symptoms. Even the immediate subjective results suggesting betterment, probably psychologic in nature, have later given way to discouragement. It is to be emphasized, however, that this series is too small and the periods of observation too short to be statistically valid.

Although it has been said (15) that in this condition the blood and spinal fluid usually show negative serologic reactions for syphilis, previous data from this clinic (8) and the observations made in this small series are in distinct disagreement with that opinion. Of the thirty-four individuals reported in Peters' and this paper, only nine (26.5 per cent) had negative blood and seven (20.6 per cent) negative spinal fluid findings, whereas serologic evidence of syphilis was present in thirty-one (91.2 per cent). In the patients reported here no significant

post-treatment improvement was noted in blood flocculation titers with the exception of Case 2; in one (Case 4) the titer significantly increased. Repeated spinal fluid examinations gave results paralleling the experience of Gammon and his associates (3) with tabes dorsalis, a closely related involvement of the spinal cord, both in regard to the observation that the more abnormal specimens underwent the greatest relative improvement and that the general serologic response appeared to be less pronounced than in the other types of neurosyphilis studied. In two instances (Cases 2, 4) a transitory pleocytosis was seen during or immediately after treatment. In no case did the spinal fluid become negative.

The therapeutic use of malaria inoculata in syphilis of the spinal cord has been condemned by some. Adams and Merritt (10) say that "it is doubtful whether malarial therapy is ever indicated except possibly in the hypothetical case with clinical improvement but persistent cerebrospinal fluid abnormalities. In such a case the malaria therapy would be indicated to prevent the development of other forms of parenchymatous neurosyphilis. It should not be given without due deliberation because of the possibility of further damage to the spinal cord." In one patient (Case 2) malarial fever therapy had been used prior to treatment with penicillin without remission of symptoms. In another (Case 3) this method was attempted in a final effort to arrest the progress of the disease. The last patient treated (Case 4) was unimproved or worse following fever therapy and penicillin given concurrently. No acute grave sequelae occurred in this series analagous to the probable spinal thrombosis reported by Adams and Merritt, but in no instance was significant serologic or clinical improvement noted following its use. Whether the benefits likely to result from malarial fever therapy outweigh the inevitable risk in patients with Erb's syphilitic spinal spastic paraplegia is doubtful.

Studies on patients with early syphilis prove that penicillin exerts a definite treponemicidal action; there is no reason to believe this is not also true for late neurosyphilis. Accumulated data (1,3,4) tend to show, however, that corresponding dosages of the antibiotic agent produce a more favorable clinical effect in cerebral syphilis than on infections which strike the spinal cord, although the processes may be basically similar in a pathologic sense. Perhaps the explanation has to

do with the ability of portions of the massive cerebrum to assume, to a certain extent, the functions of adjacent damaged areas, especially in such diffusely centered activities as consciousness, insight, memory, and speech. In the small, compact and relatively specialized spinal cord little of this can be achieved, thus accounting for the comparatively meagre responses obtained with penicillin therapy, or any other type of treatment, in this syndrome as compared with general paresis for example.

The refractory nature of Erb's paraplegia is probably explained on the basis of irreversible damage to the pyramidal tracts below the ninth dorsal segment of the spinal cord. According to King (9), the exact pathologic lesion is still in doubt. The lateral columns show degeneration below the cervical enlargement but the mechanism of this change is a mystery, possibly because there have been examined only tissues depicting end-results. Active meningomyelitis is seldom apparent on pathologic examination and the posterior columns are usually spared, both factors speaking against a general acute inflammatory reaction. Gummas within the central nervous system are not compatible with the diagnosis of Erb's spastic paraplegia. The principal vascular supply to the anterolateral columns, including the corticospinal tracts, and to the anterior horn cells, is the anterior spinal artery. The fact that amyotrophy is not a characteristic of this disease militates against involvement of this blood vessel being the sole etiologic factor. Grinker (15) has suggested that a mild arteritis and slow occlusion of the coronal spinal vessels causes gradual degeneration of the lateral columns. The so-called "syphilitic halo" of myelin sheath preparations of sections of the spinal cord is not a characteristic finding. The disease is predominately a motor one, as evidenced by clinical examinations and cystometric data, and no explanation has been forthcoming for this selective ischemia in which sensory areas are spared. In the light of this "varying pathological background" (16), it is not possible to do more than to speculate as to the precise process which finally leads to the clinical syndrome under discussion.

The material thus far reported on the therapy of Erb's syphilitic spinal spastic paraplegia is too limited to permit valid final conclusions; observation should probably be for years rather than months. These data suggest, however, that commercial penicillin mixtures, in the

amounts employed, are inadequate to cure or even to arrest the process. More work is necessary with individual penicillin fractions alone and combined with other forms of treatment before such pessimistic conclusions should be finally accepted.

SUMMARY

Four patients with Erb's syphilitic spinal spastic paraplegia are reported. Treatment consisted of intramuscular injections of commercial sodium penicillin in aqueous solution at intervals of three hours day and night for from ten to twenty five days. Total amounts employed increased from 2,000,000 to 10,000,000 Oxford units as experience showed smaller dosages to be ineffectual.

Two patients given total dosages of 3,760,000 and 6,560,000 Oxford units each were unimproved or were worse subsequent to therapy. One died 199 days following the first of two courses of 4,000,000 Oxford units, autopsy revealing anterolateral degeneration of the spinal cord, most extreme in the corticospinal tracts below the medulla oblongata. The immediate cause of death was referable to clostridial infection of extensive decubitus ulcers and was in no way attributable to penicillin administration. The most recently treated patient received 10,000,000 Oxford units of penicillin concomitantly with malarial fever therapy.

During follow-up periods of 376, 582 and 121 days after the start of therapy either lack of improvement or progression of symptoms could be seen in each of the three surviving patients. Although more data are essential before final conclusions may be drawn, these results imply that the mixtures of antibiotic substances here employed fail to improve or even to arrest the progress of this form of neurosyphilis.

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CONCERNING THE FUNCTION AND ORIGIN OF THE RETICULAR ZONE OF THE ADRENAL CORTEX

Hyperplasia in the Adrenogenital Syndrome

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It is well established that the adrenal cortex is concerned with the performance of many physiological processes in the body (1, 2, 3). Extracts of the cortex have yielded several hormones, including androgenic and estrogenic substances (4, 5, 6).

The association of certain tumors and of cortical hyperplasia with abnormal development of masculine secondary sex characteristics has long been known. The earlier case reports were summarized by Bulloch and Sequeira (7) and by Glynn (8). Gallais first described these cases as the adrenogenital syndrome (9). More recent and complete bibliography concerning the subject may be found in the book of Young (10).

The experimental work of Evelyn Howard (11) particularly, and of Deanesley (12), led to the idea that a particular zone of the adrenal cortex may be active in the metabolism of sex hormones; and Grollman postulated that the adrenogenital syndrome was due to the activity of a special "androgenic" tissue distinct from the rest of the cortex (13). Later on, however, Gersch and Grollman concluded that these pathological "androgenic effects" could be attributed either to the inclusion of embryonic testicular tissue in the adrenal or to metabolic dysfunction of the cortex (14). This conclusion was not based on the demonstration of aberrant testicular tissue or dysfunction of the anatomically normal cortex, but rather on experiments later criticized by Howard and shown by her to be inadequate as evidence against the idea that the adrenal cortex possesses a zone in which certain properties are especially well developed (11). Wilkins, Fleischmann, and Howard studied a case (case 5 of this series) which led them to suggest that the "androgenic" zone of the adrenal cortex has a function different from the part of the cortex which controls the electrolyte balance.

[1] Died October 28, 1945.

They identified the "androgenic" tissue with "prenatal zone" cells (15).

The purpose of this paper is to describe a series of 9 cases studied at autopsy in this department, and to collect from the literature evidence which indicates that the adrenal hyperplasia associated with the adrenogenital syndrome is hyperplasia of cells of the reticular zone of the cortex. There is also reason to believe that some of the adrenal tumors associated with the syndrome are of similar origin. This in turn is evidence that it is the reticular zone cells of the normal adrenal cortex which are particularly concerned with the formation of sex hormones. The cases described, together with information derived from the study of a series of adrenals of infants and children, further suggest that the post-natal reticular zone develops from cells of the foetal reticular zone which do not undergo involution and slowly maturate to comprise the adult reticular zone.

CASE REPORTS

In the following cases only those lesions will be described in detail which seem related to the conditions under consideration. There was evidence of hypertension and cardiac hypertrophy in only one of the adults (Case 9). The blood pressures of the infants were not determined, and their hearts were not enlarged at autopsy. The hypophyses of eight of the cases have been examined and will be reported at a later date.

In one case (No. 5) there was evidence of Addison's disease together with precocious development of masculine secondary sex characteristics. The concentration of electrolytes in the blood and urine of the other cases was not determined, but abnormal pigmentation of the skin or other evidence of addison's disease was not observed.

The microscopical sections were made from paraffin blocks of tissues fixed in Helly's solution and stained with hematoxylin and eosin. Other stains used were ponceau-fuchsin and aniline blue, Heidenhain's iron-hematoxylin, scarlet red, phosphotungstic acid hematoxylin, and Wilder's reticulum stain. The pancreas, ovaries and testes, and the thyroid, parathyroid, and pineal glands were all examined microscopically in most of the cases. They were for the most part essentially normal.

Case 1. This patient has previously been described by Quinby (16), and by Young as Case 25 in his remarkable series (10). She was a congenital female pseudohermaphrodite who died in uremia at the age of 31 years. Reared as a boy, and first examined at the age of ten years, an exploratory laparotomy revealed bilateral Fallopian tubes, ovaries, and a small uterus. One ovary was removed and was found microscopically to be normal. Psychological attitudes and secondary sex characteristics of the male continued to develop.

At *autopsy* (*No. 15067*), the body was short (155 cm.) and stocky. There was a heavy beard. The clitoris was large, 2.5 cm. long. The uterus was very small. The right Fallopian tube, and the left tube and ovary were present. The vagina was small and communicated with the urethra and with the perineum. There were no testes. Prostatic tissue was found about the neck of the bladder. There was widespread ulcerative colitis and extensive necrosis of renal epithelium, probably due to mercury poisoning.

The *adrenals* weighed 80 and 90 grams respectively. On section the glands in places were as much as 16 mm. thick. There were several incompletely reduplicated folds of tissue superimposed on each other. Each layer contained an outer zone of pale tissue 1 mm. or less thick. The rest of the cortical tissue in each layer was dark brown, almost black in color, and lay between the thin outer pale zone and the medulla. The latter was normal. (Plate I). Permission could not be obtained to examine the brain and hypophysis.

Microscopical Changes. The Adrenals (Plate I). The thin outermost pale zone consisted chiefly of cells arranged in parallel vertical columns, like the cells of the normal fascicular zone. These cells, however, contained no stainable lipoids (Scharlach R), no vacuoles, and no pigment. There was no distinct continuous glomerular zone, and this layer of the cortex was represented by small scattered groups of cells beneath the capsule.

The rest of the greatly thickened cortex was composed of much larger cells which were eosinophilic and also fuchsinophilic. They were arranged in long columns and irregular anastomosing cords. They contained no vacuoles or lipoids (Scharlach R). Most of them contained much more pigment than normal. The pigment was in the form of extraordinarily numerous fine yellow-brown granules which were arranged in many of the cells to form crescents or circles about the nuclei. The pigment gave negative staining reactions for iron, and was stained dark blue-black with Heidenhain's iron hematoxylin. Some of the cells contained as many as three small nuclei, and the nuclei of a few scattered cells were very large and hyperchromatic.

The ovaries both contained normal follicles with ova, small cysts, and normal stroma. The ova were numerous in the gland which was removed at operation 20 years before death, but very few were found in the ovary removed at autopsy.

Case 2. The patient was a congenital female pseudohermaphrodite, 29 years old, with a long history of masculine characteristics. She died two days after an abdominal operation.

Autopsy No. 14642. The body was short (not measured) and, except for the genitalia, resembled that of a male in every respect. The hair was thin in the frontal region and bald on the crown. There was a heavy black beard and mustache (shaved). The breasts were practically undeveloped. The chest, arms, and legs were more or less covered with thick hair. The distribution of pubic hair was masculine in type.

The labia were normal. The enlarged clitoris had been removed surgically, and was found to measure 4 x 1.5 cm. The lumen of the vagina was small, about 2 cm. in diameter and about 8 cm. long. The urethra opened into the vagina. The uterus was small (4 x 2.5 x 1 cm.). A small ovary and normal Fallopian tube were found on the right side. The left tube and ovary had been surgically removed. There was a mass of prostatic tissue 1 cm. in diameter about the urethra near the bladder, composed of groups of glands interspersed between fibers of connective tissue and smooth muscle.

The *adrenals* were greatly and symmetrically enlarged (Plate I). On section each was 1 cm. thick in places. The right weighed 30 grams. The left was similar in size. Each gland showed in places on cross section several superimposed short foldlike reduplications. Each of these layers consisted of a very thin outer pale zone about 1 mm. thick, followed by a zone of brownish-black color 2 to 3 mm. thick in each fold of tissue. The medulla looked grossly normal.

Microscopical Changes. The adrenals were alike, and were almost exactly like those in Case 1. In Case 2 there was a little more tissue in the glomerular layer than in Case 1, and the cells in the thick pigmented reticular zone were arranged in long columns, short cords and small groups which showed less evidence of branching and anastomosis than in Case 1. Most of the cells were larger than normal and were excessively pigmented (Plate I).

The ovaries contained normal stroma and corpora albicantia. The ovary removed at operation a month before death contained a few normal follicles and ova, but none were found in the section made of the ovary removed at autopsy.

Case 3. A six day old female infant pseudohermaphrodite born spontaneously at term. Three days before death she began to vomit, and for a few hours before death severe cyanosis and dyspnoea were observed.

Autopsy No. 17398. The foramen ovale was open, and was not completely covered by the valve in the left auricle. The ductus arteriosus was also patent and the lumen was about 1.5 mm. in diameter.

The clitoris was enlarged (2.5 cm. long). The large labia resembled a scrotal sac. There were no testes. The uterus, ovaries, and tubes were normal. The urethra communicated with the vagina. A small mass of typical prostatic tissues, 1 cm. in diameter, surrounded the first part of the urethra. It contained numerous groups of glands scattered in a stroma of smooth muscle and connective tissue. The urethra opened on the ventral surface of the clitoris. There was no hirsutism.

The *adrenals* were enlarged. One measured 6.5 x 4 cm. and the other 5 x 4.5 cm. On cross section each one measured 11 mm. in the thickest portion. The enlargement was seen on cross section to be due chiefly to superimposed incompletely reduplicated layers of cortical tissue. The appearance in the central part of the glands was that of several layers of cortex lying one upon the other. Each reduplicated portion was surrounded by a fibrous capsule and contained medulla enclosed by cortical tissue (Plate II).

In each of the reduplicated layers of cortex three zones could be recognized. Beneath the capsule there was thin outer pale zone less than 1 mm. thick. Beneath this a thinner darker layer was visible, and below this dark layer, next to the medulla, lay a reddish zone 1 to 1.5 mm. thick in which there were scattered minute yellow foci.

Microscopical Changes. Adrenals. Each of the individual cortical layers was, with one exception, histologically normal for an infant 6 days old. The outermost pale zone contained normal glomerular and fascicular zones. The innermost reddish zone, next to the medulla, was the involuting, foetal reticular zone of the cortex. In places the cells had disappeared leaving collapsed stroma, haemorrhages and capillaries. The yellow foci seen grossly corresponded to groups of vacuolated lipoid-containing cells (Scharlach R). Many of the large cells characteristic of the prenatal reticular zone persisted.

Between the fascicular and prenatal reticular zones there was a thin irregular layer, grossly darker than the outer glomerular-fascicular zone, and composed microscopically of small intensely eosinophilic cells whose nuclei were smaller and contained more chromatin than those of the more centrally placed larger foetal cells which had not yet disappeared (Plate II). The cells of this thin zone contained no stainable lipoids or pigment, and resembled the non-pigmented cells of the adult reticular zone.

Case 4. A colored female infant pseudohermaphrodite, 6 weeks old at the time of death. She was thought by parents and physician to be a boy with hypospadias. She began to vomit when 2 weeks old, and pyloric stenosis was supected. There was a precordial systolic murmur, and at times the child was cyanotic. She died after several hours of cough, vomiting and cyanosis.

Autopsy No. 15602. The right side of the heart was dilated. The foramen ovale was open (8 mm.), and was not quite closed by the valve. The pylorus of

the stomach was thought to be obstructed by a firm, round mass, 4.5 cm. in diameter. It looked like inspissated coagulated cream and chemical analysis showed it to contain 39% of lipoid material. There was a widespread purulent bronchitis and lobular pneumonia in each lung.

The clitoris was 11 mm. long and 6 mm. in diameter at its distal end. It was partly covered and enclosed by the enlarged labia minora which were covered by skin and resembled a redundant, partly retracted foreskin. The labia majora were enlarged and resembled a cleft scrotum. There were no testes. Fallopian tubes, ovaries, and uterus were normal. The vagina had no external opening. It communicated with the urethra by a small opening. The external urethral orifice lay on the ventral surface of the clitoris. A small nodule of prostatic tissue about 7 mm. in diameter was found in the anterior wall of the urethra above the opening of the vagina. It was composed of numerous racemose glands in a stroma of smooth muscle and connective tissue.

The *adrenals* were a good deal larger than normal. The right measured 5 x 3 cm. and the left 4 x 3 cm. On cross section through the middle they measured from 5 to 10 mm. in thickness. The appearance of each gland on section was that of folded reduplicated layers of tissue superimposed on each other (Plate II). Each of the layers contained medulla enclosed by cortex surrounded by a fibrous capsule. In each of these layers there was an outer pale zone of cortex about 1 to 1.25 mm. thick, and an inner darker reddish zone varying from a fraction of a millimeter to 2 mm. in thickness.

Microscopical Changes, Adrenals. The outer pale zone contained normal glomerular and fascicular layers and a third irregular zone composed of smaller more eosinophilic cells in the position and with the arrangement of the reticular zone of the more adult cortex. The innermost thicker reddish zone next to the medulla consisted of collapsed stroma of the foetal reticular portion of the cortex, together with many blood vessels and a few remaining large cells characteristic of the foetal reticular zone.

The cells of the postnatal reticular zone formed a layer comprising a third to a half of the cortex. They were arranged in small groups and branching, anastomosing cords, often running in a nearly horizontal direction and arranged in a way distinctly different from the long parallel vertical columns of cells in the fascicular zone (Plate II). The reticular zone cells were also quite different from the remaining cells in the involuting foetal reticular zone. They were smaller, their cytoplasm was darker red, the nuclei contained more chromatin. The cells contained no pigment or lipoid vacuoles.

Case 5. The patient was a precociously developed white boy, 3 years and 7 months old, previously described by Wilkins, Fleischmann, and Howard (15). The genitalia were unusually large at birth and continued to grow excessively. Since birth the cry and voice were deep and rough. An acneiform eruption developed on the face at the

age of 5 months and persisted. Pubic hair began to grow at the age of 15 months. There was fine down-like blonde hair on the cheeks. From an early age he had a poor appetite, and from the age of one year ate excessive amounts of salt, and had polydipsia and polyuria. Saline enemas were given frequently because of constipation.

He was admitted to the hospital for observation and study. The skin had a brownish color. The muscles were unusually well developed. The height was that of a boy 4½ years old. The development of the bones (X-ray) corresponded to that of a child 10 years old. The penis was enlarged, 7 cm. long and 1.5 cm. in diameter. Each testis was larger than normal, especially the left. There was abundant pubic hair. The voice was deep. The blood pressure varied from 90/42 to 100/80 mm. of mercury (3 determinations in 6 days). He ate little of the regular ward diet. Extra salt was not added to the food. The blood N.P.N. varied from 93.5 to 127 mg. per cent. The blood was concentrated (16.3 grams per cent). He died suddenly and unexpectedly. Blood taken from the heart immediately after death showed a marked reduction in the concentration of the serum sodium (111 m.eq. per liter). Bioassays of urine, adrenals, and aberrant adrenal tissue in the testes showed androgenic substance to be present in excess (15).

Autopsy No. 16090. The changes in the skin, muscles and external genitalia were as described above. The *adrenals* were large, weighing 12 and 15 grams respectively. On section, the cortex consisted entirely of very dark brown tissue. Each testis contained a mass of similar somewhat paler brown tissue (Plate III). The testes weighed 8 and 30 grams on the right and left sides respectively. The *prostate* was enlarged, 2.5 x 1.5 cm. on section and showed hyperplasia of the glands and smooth muscle.

Microscopical Changes: The *adrenal* medulla was normal. The cortex contained no trace of normal glomerular or fascicular zones (Plate III). None of the cells was vacuolated with lipoids like cells of the normal outer cortical tissue. The cortex, like the normal reticular zone (17), consisted of two types of cells, light and dark, arranged irregularly in masses and cords of variable size, enclosed by delicate connective tissue septa. Most of the cells were fairly large. Some showed pale coarse granular eosinophilic cytoplasm and round vesicular nuclei. Others possessed more compact, very dark eosinophilic cytoplasm and small, deeply basophilic, nuclei. The very eosinophilic cells were also stained more intensely than the paler cells by other stains, including iron hematoxylin, phosphotungstic acid hematoxylin, and the ponceau-fuchsin stain of Broster and Vines.

Many cells of both types contained fine yellow-brown pigment granules. The pigment was not hemosiderin, and resembled that found in cells of the normal adult reticular zone both in arrangement and staining properties. In many cells, the pigment formed crescents or circles at a distance from the nucleus. Many of the granules stained black or dark blue with Heidenhain's iron hematoxylin. Some, however, remained unstained, as in the normal reticular zone (18).

Testes. The masses of tissue in the testes were like the adrenal cortical tissue, and consisted of the same two types of dark and light cells. There was less pigment in these masses than in the adrenals. The tubules of the testes were pushed to the periphery, and formed narrow atrophied strands beneath the capsule. Tubular tissue was not found scattered among the hyperplastic aberrant adrenal cells. The position of the compressed testicular tubules showed plainly that the masses in the testes were not composed of interstitial cells.

Case 6. A very obese white woman with hirsutism and amenorrhoea. She was 28 years old at the time of autopsy. Pubic hair began to appear at the age of 13. At 14 her trunk and hips were larger than normal and her breasts were small. She became obese and weighed 236 lbs. when 16 years old. She first menstruated at 15, and again at the age of 16 and 17 years. Since then, the menses occurred at long and irregular intervals. At 17 hair appeared on the face and chest, and later thick coarse black hair grew over the whole body. Pubic hair was of male distribution. At 18 she fell, was unconscious for 3 days, and bled from ears and nose. Nine months later, she began to have convulsions which occurred frequently since that time. There was complete loss of libido since the age of 22. No evidence of hypertension or diabetes mellitus was ever found (she was examined by many physicians in various clinics). The clitoris was not enlarged. Two weeks after bilateral exploration of the adrenals she died from pulmonary embolism.

Autopsy No. 15873. The body was very obese (220 pounds). The adipose tissue was distributed generally over the trunk and extremities. There was soft hair over the bearded portion of the face and there was hair on the chest and lower extremities resembling that of a man. Pubic hair was masculine in type. Breasts were quite small. Clitoris was not enlarged. There were no abdominal striae.

The heart was somewhat hypertrophied and weighed 400 grams, probably due to obesity. The left adrenal when completely freed of surrounding adipose tissue, was enlarged, weighed 17 grams, and measured 7 x 5 x 1.5 cm. On section the outer cortex was yellow, about normal in appearance. The reticular zone was unusually prominent, very dark brown in color, and variable in width. In

some places it was thicker than the glomerular and fascicular zones together (Plate IV). The right adrenal was swollen, largely necrotic, as a result of thrombi in its blood vessels. On section, however, it could be seen that there was no tumor and that the brown reticular zone was thicker than normal.

In the inferior tip of the 4th cerebral ventricle, attached to the roof, a small tumor nodule, 5 mm. in diameter, was found. The ventricles were not dilated in front of the tumor. The latter proved microscopically to be an astrocytoma. There was an old decompression wound in the right parietal area and the meninges beneath were adherent. This lesion was probably responsible for the convulsions mentioned above.

Microscopical Changes. Left adrenal. The glomerular and fascicular zones were normal. Lipoid vacuoles were numerous, especially in cells of the fascicular zone. The reticular zone was thicker than normal. The cells were normal in size. Most of them contained fine pigment granules, and in many there were a few small lipoid vacuoles. The reticular zone was somewhat oedematous and there were scattered microscopical hemorrhages in it.

Ovaries. Both ovaries contained several small follicular cysts, corpora albicantia, and small numbers of normal follicles. In one ovary there was a corpus luteum.

Vertebra. In a section of one vertebra there was evidence of osteoporosis. The spicules of cancellous bone were slightly but distinctly thinner than normal.

Case 7. The patient was a woman 34 years old. She was treated in the hospital for only 2 days, and died with widely disseminated lesions of periarteritis nodosa. Menstrual history was not investigated.

Autopsy No. 17805. There was a well developed growth of hair on the upper lip, and a stubble of beard on the chin which had been shaved. Pubic hair extended to the umbilicus. The duration of the hirsutism was not determined. The breasts, uterus, ovaries, tubes and vagina were grossly normal. The clitoris was not enlarged.

The *adrenals* were a little enlarged. The right weighed 10 grams and measured 7 x 5 cm. The left weighed 12 grams and measured 9 x 4 cm. On section each leaf of tissue was 5 mm. thick, and showed an outer yellow zone 1 to 1.5 mm. thick, a dark brown reticular zone which was everywhere as thick as the outer yellow zone and in some areas was thicker. The medulla was of normal size.

Microscopical Changes. Adrenals. The amount of tissue and the appearance of the cells in the glomerular and fascicular zones were normal. Most of the cells of the fascicular zone were almost filled with lipoid vacuoles. The reticular zone was distinctly thicker than normal (Plate IV). The cells were normal in size. They were eosinophilic, fuchsinophilic and contained only a few stainable lipoids. Most of the cells, especially those in the deeper parts of this zone, contained very fine granules of yellow-brown pigment. In some cells pigment could not be recog-

nized. *Ovary.* The routine section of one ovary contained small follicular cysts, but there were no normal follicles with ova.

Case 8. The patient was a woman 47 years old with hirsutism and a history indicating the presence of a brain tumor for about one month. The menses had always been regular, and in recent months had increased in volume. She died an hour after partial removal of a large spongioblastoma which involved the right temporal lobe, the midbrain, cerebellum, and pons on the right side.

The *autopsy* (*No. 18445*) showed a good deal of coarse black hair on the upper lip and a few similar hairs on the chin. No other hirsutism was described. The clitoris was not enlarged.

The adrenals were normal in shape and size. The brown reticular zone, however, was everywhere thicker than normal, and in places was as thick as the glomerular and fascicular zones together.

Microscopical Changes. Adrenals (Plate IV). The glomerular and fascicular zones were normal. Most of the cells of the fascicular zone were largely occupied by lipoid vacuoles. The reticular zone consisted of two types of cells, "light" and "dark," which were eosinophilic and also fuchsinophilic. The cells of the outer portion of the reticular zone were arranged in parallel columns, like the cells of the neighboring fascicular zone, and some of these cells contained a few large lipoid vacuoles. Many of the reticular zone cells contained very fine yellow-brown pigment granules.

Ovary. In the routine section there were corpora albicantia, and a few normal follicles.

Case 9. The patient was a white girl, 20 years of age, with signs and symptoms for about two and a half years which suggested Cushing's syndrome. (Amenorrhoea, decrease in size of breasts, obesity of face, trunk, and thighs, hirsutism, hypertension, and abdominal striae.) Unhappy over her condition, she drank and aspirated formaldehyde, developed abscesses in the lungs, and died from abscesses in the brain.

On examination 9 days before death, the typical "buffalo" type of obesity was observed, together with plethoric appearance, long reddish abdominal striae, moderate hirsutism (face, abdomen, and extremities), and hypertension (155/110 to 190/120). The urine contained no sugar or protein. The blood sugar was normal (86 mg. per cent), and the sugar tolerance test was normal. The basal metabolic rate was −3. The bones were not x-rayed.

Autopsy No. 18626. The body was short (150 cm.) and weighed 140 pounds. The legs and arms were thin, while the thighs, torso, and neck appeared fat.

There was hair on the face, chest, arms, legs, and lower abdomen. Striae were seen in the abdominal wall and thighs. The breasts were about normal in size. The clitoris was not enlarged.

The heart weighed 300 grams, and the left ventricle was a little hypertrophied. There was very little atherosclerosis of the aorta. The mesenteric fat was thick.

The adrenals were normal in size and weight (8 and 10 grams). The outer cortex was yellow in color and about 1 mm. thick. In each gland the brown reticular zone was considerably thicker than normal, measuring 1 to 1.5 mm. This zone was mottled and distinctly paler in one adrenal than in the other (Plate IV).

The pelvic organs, including the ovaries, were grossly normal. Aside from abscesses in the right lung, and in the brain, no other significant gross lesions were found.

Microscopical Changes. Adrenals. In each adrenal the eosinophilic, fuchsinophilic, reticular zone of cells was irregular in width. It was everywhere as thick as the outer glomerular and fascicular zones together, and in places it was thicker. Many cells of the reticular zone contained characteristic fine yellow-brown granules but the amount of pigment was not excessive. In many areas straight columns of cells of this type extended far out into the fascicular zone. In one of the adrenals there were a good many fine hyaline scars scattered irregularly in the reticular zone. None were present in the other adrenal. There was no inflammatory reaction in the scars, and no cause for them was discovered. Numerous large lipoid vacuoles were present, particularly in the cells of the fascicular zone. The medulla was normal.

Other Microscopical Lesions. The glandular tissue of the breast was atrophic, and the surrounding connective tissue increased. Very few follicles were found in the ovaries. A section of one vertebra showed osteoporosis of moderate degree. The intima of the coronary arteries was moderately thickened. There were a few hyaline arterioles in the pancreas. Serial section of the hypophysis disclosed a small basophilic adenoma in the anterior lobe, 4 mm. in diameter.

Kidneys: The main renal arteries and their hilar branches were not sclerotic. There was slight thickening of the intima of a few interlobular arteries. No hyaline arterioles were found.

Scattered irregularly in the cortex were moderate numbers of tubules containing laminated casts of necrotic, hyaline cells and pyknotic nuclei. Some of these tubules were dilated, and some were moderately atrophied. The changes were characteristic of those seen commonly now following sulfonamide medication, and the patient had received intravenous sodium sulfadiazine.

STRUCTURE OF THE NORMAL ADRENAL CORTEX

The normal adrenal cortex is composed of three layers of cells. The two outermost layers, the glomerular and fascicular zones, are grossly yellow due to lipoid deposits in the cells. The lipoids are represented in paraffin sections by vacuoles in the cells. The outer or glomerular

layer is very thin, and the cells are arranged in a characteristic pseudoglandular fashion. The middle or fascicular layer is thick, comprises the bulk of the cortex, contains most of the lipoids in the gland, and the cells are arranged in long parallel columns separated by capillaries and collagen and reticulum fibers.

The innermost or reticular layer of the adult gland forms a distinct thin brown zone between the outer yellow layers and the white central medulla.[2] Microscopically the outermost cells of the reticular zone are not sharply separated from the deepest cells of the fascicular zone, but blend gradually with them. The cells of the reticular zone, especially those nearest the medulla, form irregularly arranged, anastomosing cords, and other small rounded groups inclosed by reticulum fibers. Many of the cells, beginning at about the age of puberty, contain fine granules of yellow-brown pigment, and they lack the numerous large lipoid vacuoles which fill the cells of the fascicular layer of the cortex. The dark color of the reticular zone is due to the small amount of lipoid, to pigment in the cells, and to the presence of wide blood capillaries between them.

Two types of cells are present in the reticular zone, "dark" and "light" cells (17). The majority are coarsely granular, pale, eosinophilic cells. The others, present in smaller numbers, are smaller cells with more eosinophilic cytoplasm, and they possess small hyperchromatic nuclei. Pigment may be found in cells of both types. The pigment is not hemosiderin, and when appropriately stained gives negative reactions for iron.

The origin, chemical nature, and functions, if any, of the pigment are not known (18). The pigment granules are said to be precipitated on pre-existing mitochondria, and both mitochrondria and pigment granules may be arranged in a characteristic circular or crescentic fashion about the nuclei. Both may be stained readily by means of iron hematoxylin but usually some remain unstained (18). The presence of pigment serves in the normal adult reticular zone, and under abnormal conditions as well, to identify reticular zone cells and to differentiate them from cells of the glomerular and fascicular zones. The absence of numerous lipoid vacuoles is another characteristic of these cells.

[2] The medulla is not brown or reddish-brown, as described by some authors (17, 19).

Reticulum stains bring out in a striking manner the differences between the arrangement of cells in the reticular and fascicular zones. In the reticular zone small rounded groups of cells, and even single cells are surrounded by reticulum fibers. The cells of the fascicular zone tend to form long double columns separated by fibers of reticulum.

The reticular zone of the adult cortex corresponds in position to a much thicker transient zone of larger cells in the embryo and new born infant. This latter zone is spoken of in the literature as the foetal, prenatal, androgenic or X-zone. The idea has been more or less generally accepted that it corresponds to a transient zone in the adrenal of the mouse named the X-zone by Howard (20), and on this account the term X-zone is also frequently used to designate the transitory zone of the human foetal adrenal. In the mouse the transient zone does not become fully developed until about 2 weeks after birth, and disappears at about the age of 5 weeks in the male and later in the virgin female (20). Originally it was recognized to be the reticular zone (21), and when the term X-zone was later applied by Howard she stated that it was a highly developed reticular zone.

It seems much simpler and preferable in every way to speak of this zone in man as the *foetal reticular zone*. In position it is the same as that of the adult reticular zone, and the cells of the foetal reticular zone do not differ from those of the adult reticular zone any more strikingly than the cells of the foetal glomerular and fascicular zones differ from those in the corresponding adult zones.

The cells of the human foetal reticular zone at birth, and even in the foetus as young as 10 weeks, are large and look mature when compared to the very small cells of the glomerular and fascicular zones. In fact the cells of the foetal reticular zone resemble in a striking manner those of the adult human liver both in the arrangement of cells to form tortuous anastomosing cords separated by wide sinusoidal capillaries, and also in the size and appearance of individual cells. The cells and their nuclei when measured are almost identical in size with adult liver cells. The cytoplasm is coarse, granular, and eosinophilic. Nuclei are vesicular, and each possesses a large nucleolus.

Most of the cells of the foetal reticular zone undergo necrosis and disappear within a month after birth, and by the end of the first year of life this process of involution, as it is commonly called, is generally agreed to be completed (22, 23). The normal post-natal reticular zone

cells are smaller than those of the foetal zone, and their nuclei are smaller and contain more chromatin. The cells of the foetal reticular zone do not contain the pigment which is so characteristic of many of the cells of the adult zone. Pigment does not generally appear in the cells, however, until about the age of puberty. Lipoid deposits in the post-natal reticular zone are much less abundant than in the fascicular zone above. The arrangement of reticulum fibers around single cells and small groups of cells is also similar in both prenatal and postnatal reticular zones, and is strikingly different from the distribution of reticulum in the rest of the cortex.

THE ORIGIN AND DEVELOPMENT OF THE ADULT RETICULAR ZONE OF THE ADRENAL CORTEX

Conflicting views are expressed in the literature concerning the origin and development of the postnatal reticular zone of the adrenal and very few studies have been directed toward this particular point. Howard found that the "juvenile cortex" of the rat, which corresponds to the foetal reticular zone in the human, is gradually transformed into the adult reticular zone by the age of 40 days (24). In a recent review of the adrenal-gonad relationship Parkes states that by the end of the second postnatal month the human adrenal possesses the essential structural features of the adult gland, "the foetal cortex having given place to the zona reticularis" (25). It was observed long ago by Cooper that the three zones of the cortex are well defined by the second month after birth (26).

Grollman however, says that at birth there is in man a large zone (his "androgenic" zone) between the reticularis and the medulla (13), which indicates that in his opinion the reticular zone is present at birth and is different from his "androgenic" zone. Lewis and Pappenheimer concluded from their studies that no growth of the human adrenal cortex takes place during the first three years of life (22), and it is said by Maximow and Bloom that the reticular zone develops during the third year (17). The recent studies of Benner have demonstrated however that a steady growth of both cortex and medulla takes place throughout infancy and childhood (23). The development of the different zones of the cortex was not investigated by her.

A good many authors have stated that the adrenal cortex grows from without inward, that the innermost reticular cells die and are replaced by cells which have pushed in from the outer parts of the cortex. The predominant germinative rôle has been variously attributed to "indifferent" cells in the capsule, cells of the glomerular layer, and to fascicular zone cells (27). Hoerr, who made an experimental study of the matter, stated that the idea of a constant inward movement of the cortical cells rests upon two things, cell division in the outer cortex and cell necrosis in the inner zone. Hoerr himself, however, found mitotic figures in the reticular zone of guinea pigs after chloroform poisoning, and this shows clearly that reticular zone cells are capable of regenerating (28). The fact that mitotic figures were more numerous in the fascicular zone is not sufficient evidence to demonstrate that cells of this zone migrate to form the reticular zone.

The assertion that cells from the outer part of the cortex are the ones that multiply and by their migration inward form the reticular zone has never been demonstrated, as a matter of fact, and the idea is said to date back to Gottschau who, in 1883, expressed not only this opinion concerning the origin of the reticular zone, but also considered the reticular zone and medulla to be a single "zona consumptiva," and upheld the view that the medulla arose from the cortex (20).

In view of these divergent opinions concerning the origin of the postnatal reticular zone, a series of 150 adrenals was examined during the course of this study. They were obtained at autopsy from foetuses 10 to 14 weeks old and from infants, children, and adolescents who varied from 2 hours to 18 years in age.

It was found first, in agreement with previous similar studies, that by the end of the first month of postnatal life the majority of the cells of the foetal reticular zone have disappeared. A few scattered large cells, typical of this zone, were found, however, in some children as old as 3 years. It was further found that a very narrow irregular zone of foetal reticular cells, lying next to the fascicular zone, had by the end of the first week of life become different in appearance from the larger, more centrally located, involuting cells. They were smaller, more eosinophilic, and the nuclei contained more chromatin. The differentiation of these cells as a distinct zone was evident in the adrenals of all of the children 7 days or more in age.

In the infants less than a week old the cells of this zone clearly represented the outermost layer of the foetal reticular zone. With increasing age they persisted and gradually were transformed into a zone of cells smaller than the more central involuting foetal cells, more eosinophilic and smaller than the cells of the fascicular zone with which they blended. They contain much less lipoid (Scharlach R) than cells of the vascicular zone. Pigment was found in some of the reticular zone cells of children as young as 12 years of age.

Reticulum stains were made of sections of 45 of the adrenals of this series. The persistence and differentiation of the peripheral cells of the prenatal reticular zone, and the development of this zone to form the postnatal reticular zone could be followed with particular clarity by means of the silver stain. The cells were easily identified by the presence of reticulum surrounding single cells and small rounded groups of a few cells.

From the age of about six weeks to three years the reticular zone was found to form a very thin layer of irregular width. In general it was nor more than a few cells deep, but the characteristic arrangement of reticulum about single cells and small groups of cells made the recognition of this zone unmistakable. After the age of three years the zone became gradually thicker, and by the age of eighteen years it comprised about one fourth of the width of the cortex.

This series of 150 cases indicates that the normal postnatal reticular zone originates at an early age from persistent cells of the foetal reticular zone which fail to undergo involution. As the infant grows the cells differentiate gradually to assume the morphological features of the more adult type of cell. Such an origin of the adult reticular zone is also indicated by the presence of hyperplastic reticular zones in the abnormal adrenals of the infant and adult pseudohermaphrodites described above.

THE RETICULAR ZONE OF THE ADRENAL CORTEX AND THE ADRENOGENITAL SYNDROME

It has been suggested that the adrenogenital syndrome is due to failure of involution and subsequent hyperplasia, or to tumor formation of that part of the foetal cortex which normally disappears; and it has been said that the hyperplastic tissue proliferates and ultimately assumes malignant characteristics (29).

The adrenals of the two infant pseudohermaphrodites described above contained post-natal reticular zones which were thicker than normal. They also possessed foetal reticular tissue in stages of involution which was normal in degree for the age of each infant. In the older patients, two of whom were female pseudohermaphrodites, 29 and 31 years of age, the hyperplastic cortical tissue was composed of adult reticular zone cells, identified by their content of pigment; and there was no evidence of "degeneration into a malignant process" (29), even after 29 and 31 years.

It is evident in these four pseudohermaphrodites, however, that aside from hyperplasia of the post-natal reticular zones the adrenals were also malformed. The cortical layers were unduly reduplicated, and to this extent the foetal reticular zones especially must have been present in excessive amounts. Since the malformations of the genitalia evidently existed from a very early period of embryonic life, it is probable that they were due at least in part to the excess of foetal reticular tissue, insofar as they were caused by adrenal influence at all, because the reticular zone comprises the bulk of the foetal cortex. The continued progressive development of pseudohermaphroditism in the older patients was clearly associated with extreme hyperplasia of reticular zone tissue and diminishing numbers of glomerular and fascicular zone cells. These cases suggest that both the foetal and post-natal reticular zones perform functions connected with the development of masculine secondary sex characteristics. The evidence cited above to show that the post-natal reticular zone develops from remnants of the prenatal reticular zone is pertinent in this connection.

The patient represented by Case 5 above not only developed adult type of male secondary sex characteristics at a very early age, but also presented classical signs and symptoms of Addison's disease. The enlarged adrenals and the accessory cortical masses in the testes were composed of hyperplastic, pigmented, reticular zone cells. The absence of any recognizable glomerular and fascicular zone tissue was apparently responsible for the presence of Addison's disease. This case, therefore, like the others, indicates the existence of a causal relationship between hyperplasia of reticular zone tissue and the adrenogenital syndrome. It also indicates as already pointed out (15), that the different layers of the adrenal cortex may perform separate functions.

The fact that the reticular zone cells of the adrenal cortex are morphologically distinct in many ways also suggests that they may possess specific functions. Early studies of Goormaghtigh led him to the conclusion that one of the functions of the reticular layer was connected with development and growth of secondary sex characteristics (30). The association of hyperplasia of reticular zone tissue with excessive development of masculine secondary sex characteristics in the cases described above, supports this idea, and a number of similar cases have previously been recorded in the literature.

Flynn described a case in which there was hirsutism, excessive urinary excretion of 17 ketosteroids, and hyperplasia of the reticular zone of the adrenal (31). Goldzieher and Koster reported 5 examples of virilism characterized by hirsutism, amenorrhoea, obesity and hyperplasia of the adrenal reticular zone (32). In one of the patients hypertension was also present. Broster, Hill and Greenfield reported on four cases of the adrenogenital syndrome without tumors. All four showed abnormalities of the reticular zone of the adrenal cortex. In three the reticular zone was hyperplastic, and in the fourth case abnormal pigmentation was all that was recognized (33). In the case reported by Wilkins, Fleischmann, and Howard (15), (Case 5 of the present series), and in the cases described by Young (10), the hyperplastic cortical tissue was called androgenic tissue, and the authors were not particularly concerned with specific identification of the cells. Wilkins, Fleischmann, and Howard, however, clearly described the dark brown color of the enlarged adrenals, and the photograph of the adrenals of Case 25 in Young's series also shows the dark almost black color, characteristic of adult reticular zone tissue (Case 1 of this series).

These cases of cortical hyperplasia from the literature and the series reported in this paper, show clearly that the adrenogenital syndrome is frequently associated with hyperplasia of adrenal cortical cells which are histologically identifiable with those of the reticular zone; and it is also clearly indicated by these cases that the cells of the post-natal reticular zone are not identical with cells of the foetal reticular zone at birth, although the former develop and differentiate from the latter.

Varying degrees or manifestations of the adrenogenital syndrome have frequently been seen in association with tumors of the adrenal. The tumors have rarely been described as being browh in color, and

pigmentation of the cells has not been mentioned in most of the cases. It has been difficult to identify the tumor cells precisely with cells of any specific cortical zone. This is readily understandable, and is probably due to the well known fact that tumor cells in general tend to vary slightly or even extremely from the cell type of origin.

It is therefore significant in this connection that, despite this difficulty, some of the tumors have been recognized as being composed of, or as containing, cells which resembled those of the normal reticular zone; and the descriptions of other tumors given by the authors suggest a resemblance to reticular zone tissue. Such examples may be found in the reports of Broster and Vines (34, 35), Simpson and Joll (36), Howard and Whitehill (37), Lukens and Palmer (38), and in the earlier papers of Cahill and his associates (39, 40, 41).

In his earlier papers Cahill specifically stated that the cells of the tumors resembled reticular zone cells more than cells of the outer cortex. In reporting a later series, however, he concluded that the tumors contained cytoplasmic lipoid vacuoles in amounts roughly comparable to the endocrine symptoms (42). Lipoid vacuoles in cells of adrenal tumors would obviously suggest a resemblance to cells of the fascicular zone, and, in fact, a good many tumors of this kind have been reported as hypernephromas. It is evident from the text of Cahill's paper, however, and from the accompanying photographs that some of the tumors with vacuolated cells also contained cells without vacuoles, and some of the photographs show no vacuoles in the cells (42).

Simpson and Joll described an adrenal tumor in a man of 34 years associated with excessive excretion of estrogenic hormone in the urine. The tumor cells in places were arranged like the three zones of the normal cortex, and throughout the bulk of the tumor a structure resembling one or other of the normal zones was recognized.

In a case of virilism of a woman reported by Howard and Whitehill, an adrenal tumor, 9 cm. in diameter, was removed surgically, and was observed to be light brown in color for the most part. Some areas were much darker. The gross appearance of this tumor suggests reticular zone tissue, but pigmentation of the cells was not described.

Lukens and Palmer described a similar case of female virilism in which the tumor was reddish-brown in color. Only a small amount

of lipoid was found microscopically and pigmentation of the cells was not mentioned.

It is evident from the literature that most of the tumors found in association with the adrenogenital symdrome have not resembled the reticular zone to the extent of being obviously brown in color; and even in those few cases in which the tumor was grossly brown, pigment, if present, was evidently not plentiful enough to be a striking microscopical feature. The descriptions of the tumors suggest, however, that in many cases vacuolated cells resembling the fascicular zone and also cells without vacuoles which might represent slightly or non-pigmented reticular zone cells were both present.

It is generally recognized that the normal urine of individuals of each sex contains androgens and estrogens; and it has been repeatedly observed that estrogens or androgens, depending on the type of disorder, may be excreted *in excess* by patients with the adrenogenital syndrome. No attempt will be made to refer to all of the case reports bearing on this aspect of the subject. Many of them may be found by consulting the papers of Crooke and Callow (43), Wilkins, Fleischmann, and Howard (15), Talbot, Butler, and Berman (44), Wintersteiner (5), and Parkes (25).

The cases described above and those summarized from the literature indicate that the adrenogenital syndrome and its associated excessive excretion of sex hormones are phenomena closely related to hyperplasia or tumors of reticular zone cells of the adrenal cortex. From this it may be concluded that the androgenic and estrogenic functions of the normal adrenal cortex are probably carried out by cells of this zone.

EXPERIMENTAL EVIDENCE CONCERNING THE FUNCTION OF THE RETICULAR ZONE IN ANIMALS

The idea that a specific tissue in the adrenal is involved when disturbances in the sex characters exist is further suggested by the fact that many tumors of cortical origin are not accompanied by any recognized endocrine disorders. Experimental evidence indicates that the cells of the reticular zone represent such a specific tissue.

It was found by Zalesky that the adrenals of squirrels increase in size and weight during the breeding season, due to expansion and differentiation of the reticular zone (45). Experiments of Price and those of

Howard have shown that in the newborn castrated rat, unlike the castrated adult, the prostate continues to grow for some weeks, associated with and probably due to hyperplasia of the inner (reticular) zone of the adrenal cortex (46, 47, 24). In the young female rat the rudimentary prostate continues to develop as long as the "juvenile" cortex, which is the foetal reticular zone, persists. After this period, a matter of 40 days, both the prenatal or "juvenile" part of the cortex and the prostate regress (48).

Castration of adult mice results in atrophy of the seminal vesicles; but castration of young mice is followed by continual development of the seminal vesicles. This is due to hyperplasia of the X zone of the adrenal cortex (the foetal or juvenile reticular zone) because the effect on the seminal vesicles is prevented by adrenalectomy, (49, 50).

This experimental evidence indicates that in rats and mice the foetal reticular zone of the adrenal cortex, which persists for some time after birth in the young animal and is spoken of as the juvenile cortex or X zone, is especially active in relation to certain secondary sex characters. The development of this zone in mice has been prevented by the administration of male sex hormone (51, 52, 53, 54).

THE PONCEAU-FUCHSIN STAIN IN RELATION TO THE ADRENAL CORTEX

Broster and Vines and their associates have studied tumors and portions of adrenals removed surgically in which there were no demonstrable tumors in association with the adrenogenital syndrome (33, 34, 35). The tissues were stained by means of ponceau-fuchsin and aniline blue. The technique employed by Broster and Vines in using the stain was essentially that described in 1928 by Masson (55). It was subsequently modified by Foot (56), and is well known as Masson's trichrome stain.

It was concluded by Broster and Vines that in cases of the adrenogenital syndrome associated either with hyperplasia or tumor of the cortex, a fuchsinophilic material was present in the cells of the cortex or neoplasm, and was absent or present in only a few cells of the normal adrenal and in adrenal tumors not associated with endocrine disorders. This work has led to rather wide acceptance of the idea that fuchsinophilic staining of cells in the adrenal cortex is evidence of a specific masculinizing hormone.

This conclusion as such is probably unjustified, and may possibly

be explained by unfamiliarity with the wide staining powers of the ponceau-fuchsin stain. It should therefore be pointed out that the ponceau-fuchsin of the trichrome stain, whether the technique employed be that of Masson, Foot, or Broster and Vines, has affinity for cell cytoplasm in general, and cells that are stained red by eosin are also stained by fuchsin. Ponceau-fuchsin is a somewhat more intense stain than eosin, and it makes the granular character of cell cytoplasm in general more conspicuous than does eosin. The stain as used by Broster and Vines colors many different types of cells red, such as renal tubular epithelium, liver cells, pancreatic acinar tissue, muscle and many other cells.

We have used it to stain sections of the adrenals removed at autopsy from many individuals of widely varying age and of both sexes. The fat-laden cells of the normal adrenal fascicular zone contain little cytoplasm that is either eosinophilic or fuchsinophilic because the cells are largely occupied by vacuoles of lipoid. The post-natal reticular zone cells and the foetal reticular zone of the cortex of the premature and new born infants are regularly stained red by fuchsin as by eosin. The "dark" cells of the reticular zone are more deeply stained than the "light" cells.

It is difficult to understand why Broster and Vines found such a scanty distribution of fuchsinophil cells in the adrenals of their series of autopsied cases without virilism (one out of twenty-two under forty years of age). The cells which they did stain by fuchsin, however, were mostly in the reticular zone.

It has been found in the course of the present study that even the glomerular and fascicular zones of the adrenal are stained red by the ponceau-fuchsin when the lipoid materials have disappeared from the cells; and it has been known for a long time that in many infections, even of short duration, such as lobar pneumonia, the lipoids in the adrenal cortex may quickly diminish (57).

The adrenals of the 9 cases reported above were stained by the ponceau-fuchsin method of Broster and Vines. The results were essentially the same in each case. The reticular zone cells and the muscular walls of blood vessels were stained red by the ponceau-fuchsin, and the connective tissue blue. In the cases in which the glomerular and fascicular zone cells lacked lipoid vacuoles, these cells

also were stained by the ponceau-fuchsin. When the outer cortical cells were laden with lipoid the vacuoles were unstained, and the scanty cytoplasmic granules between the vacuoles took the stain whether ponceau-fuchsin, eosin, phosphotungstic acid hematoxylin, or iron hematoxylin was used.

It was also found that technically the stain as recommended by Broster and Vines was not always satisfactory. Differentiation was not always uniform, and occasionally even connective tissue fibers retained the fuchsin instead of the aniline blue.

The specificity of the ponceau-fuchsin stain has also been doubted by others. Flynn, referred to above, in studying the hyperplastic reticular zone of his case, found that Vines' ponceau-fuchsin stain did not display any advantage over eosin (31). Cahill has also expressed uncertainty concerning the specificity of the stain (40, 42). Uotila studied the staining reaction of the adrenal cortex in the fowl (58). He pointed out that Broster and Vines in their original monograph did not give directions for making up the ponceau-fuchsin stain, which is evidence that the results of the stain do not depend on very precise technique (34). In his own studies Uotila made use of 1% solution of Grübler's ponceau-fuchsin in 1% acetic acid. He also used Foot's modification of Masson's trichrome stain, and concluded that no proof exists that "the fuchsinophile reaction is specifically correlated with the alleged masculinizing hormone or function of the adrenal cortex." Uotila also found that sympathetic ganglion cells, smooth muscle, and many other cells besides those in the adrenal cortex were stained by ponceau-fuchsin.

Broster and Vines expressed their results by saying that in positive cases the cells contained fuchsinophilic material, which really means, of course, only that the cells were stained red by fuchsin. Sudds, on the other had, looked for discrete fuchsinophilic granules, and found them to be present in 25 per cent of the adrenals of a series of 208 autopsies. No granules could be stained in the adrenals of either sex under the age of 20, and when present they were most numerous in cases with severe infections. None were found in adrenals of 20 mice, but they were stained in "the deep cortical zone" of both male and female guinea pigs.

The studies of Sudds indicate clearly that the normal human adrenal

cortex possesses no specific fuchsinophilic granules comparable, for example, to the granules in the cells of the anterior lobe of the hypophysis. She concluded that sex plays no part in determining the presence of fuchsinophilic granules in the adrenal (59).

It is evident that in the normal adrenal the cells of the reticular zone are the most fuchsinophilic, just as they are also the most eosinophilic, and for the same reasons (lack of numerous large lipoid vacuoles). These cells, however, are no more fuchsinophilic or eosinophilic than the cells in many other tissues of the body, including cells of the outer adrenal cortex in the absence of lipoid vacuoles. The predominance of fuchsinophilic cells in the adrenals of the series of 36 cases reported by Broster and Vines suggests, however, that in their cases, too, the adrenogenital syndrome was associated with hyperplasia of reticular cells, since ponceau-fuchsin, eosin, and most other stains, when applied to the adrenal cortex, color particularly those cells which lack numerous large lipoid vacuoles, i.e., the cells of the reticular zone.

SUMMARY

1. Nine autopsied cases are described which illustrate various manifestations of the adrenogenital syndrome.

2. The series includes four female pseudohermaphrodites (two infants and two adults), two adult women with hirsutism, a woman exhibiting hirsutism, obesity, amenorrhoea, and atrophy of the breasts, a girl of 20 with Cushing's syndrome, and a boy three and a half years old in whom precocious development of secondary sex characteristics had been observed to progress since birth.

3. In all of the cases there was hyperplasia of the reticular zone of the adrenal cortex which varied in degree from slight to extreme in the different cases. In one case both adrenals and accessory cortical tissue in each testis consisted entirely of hyperplastic reticular zone tissue. In addition to the adrenogenital syndrome the patient manifested and died from Addison's disease, due to the lack of glomerular and fascicular zone cells.

4. Study of the adrenals of two infant pseudohermaphrodites, 6 days and 6 weeks old, and of a series of adrenals of 150 other infants and children, showed that the post-natal reticular zone is formed in

the first few days of extra-uterine life by differentiation of a peripheral zone of cells in the foetal reticular zone. The post-natal reticular zone in the adrenals of the infant pseudohermaphrodites was hyperplastic, while the foetal reticular zone in each exhibited the normal degree of involution.

5. The brown pigment characteristic of many cells in the adult reticular zone does not ordinarily appear in the first few years of life, and was not present in the hyperplastic reticular zones of the infant pseudohermaphrodites. The hyperplastic reticular zone was pigmented in the other seven cases of the series, and in the gross specimens it was consequently thick and brown in color, like the thin reticular zone of the normal adult cortex.

6. The reticular zones in the adrenals of two adult pseudohermaphrodites were extremely thick. The cells were much larger and contained much more pigment than normal. Relatively little tissue remained in the glomerular and fascicular zones, and the remaining cells contained little stainable lipoid. It is probable that Addison's disease would eventually develop in such cases as the glomerular and fascicular zones become replaced by progressive hyperplasia of the reticular zone cells.

7. The ponceau-fuchsin stain of Broster and Vines is essentially Masson's trichrome stain, and is not specific for cells of either the normal or hyperplastic adrenal cortex. In general it stains cells which are also stained by eosin. The most fuchsinophilic, as also the most eosinophilic cells in the normal adrenal cortex are those of the reticular zone, and this is due to the fact that the cytoplasm of these cells contain little of the lipoids whose vacuoles fill the cells of the fascicular zone.

8. In the presence of various diseases which cause the lipoids to disappear from the cells of the outer adrenal cortex, these cells become filled with cytoplasm which is then stained by eosin and also by ponceau-fuchsin.

9. Evidence collected from the literature and from the present series of cases indicates that the different zones of the adrenal cortex may perform separate functions. The evidence suggests that the reticular zone (prenatal and postnatal) is concerned especially with the metabolism

of masculinizing sex hormones, and that control of electrolytes is a function of the outer layers of the cortex.

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PLATES

PLATE I

Top: Gross adrenals, Cases 1 and 2. The enlarged adrenals consist mostly of thick, pigmented, reticular zone tissue.

Middle: Adrenals, Cases 1 and 2. Approximately the inner two-thirds of the cortex consists of hyperplastic reticular zone tissue.

Bottom: Adrenal reticular zone cells, Cases 1 and 2. Oil immersion. Hematoxylin and eosin stain. Pigment granules are very numerous.

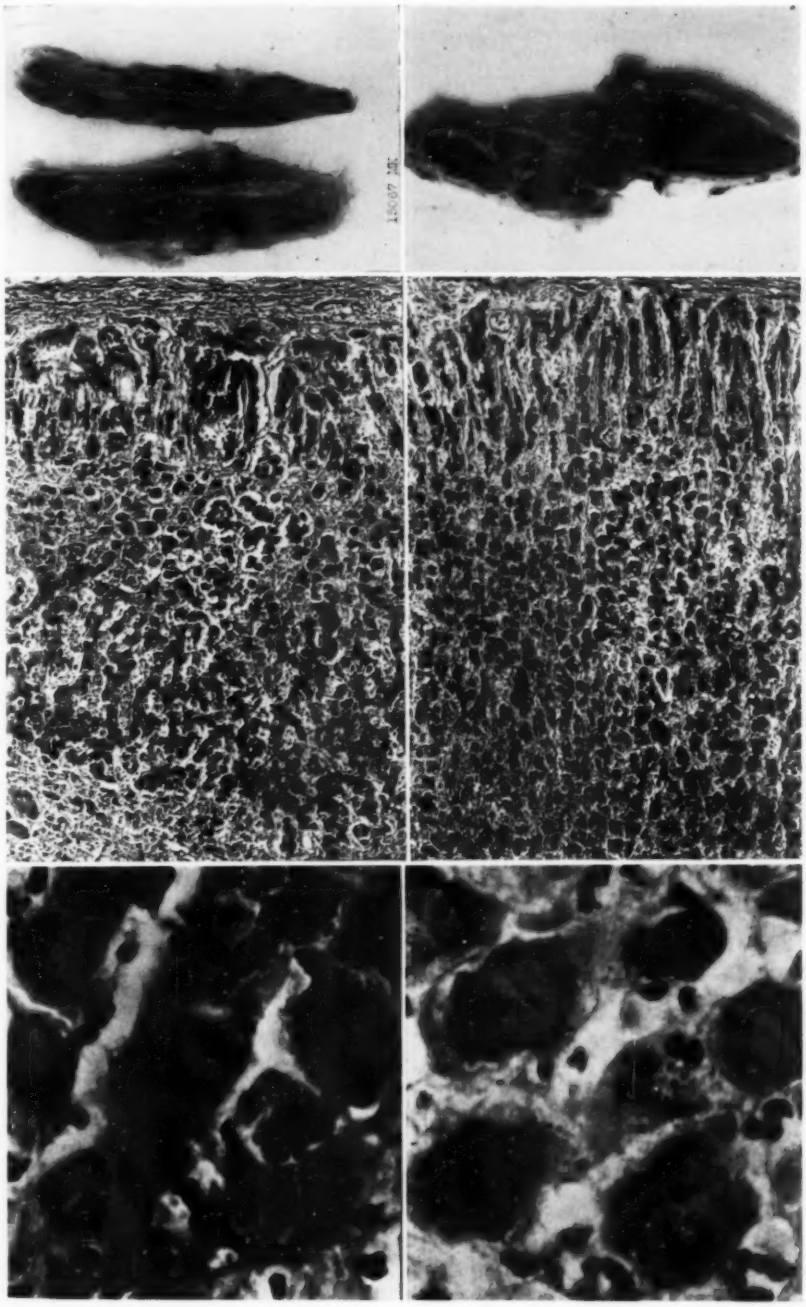

PLATE II

Top and Middle pictures show the adrenals of Case 3. Note the multiple superimposed layers of cortex, and (middle) the prematurely developed adult type of reticular zone, which in the photograph forms a zone of deeply stained cells between the outer glomerular-fascicular zones and the inner prenatal reticular zone.

The two pictures at the bottom show the adrenal from Case 4. Multiple superimposed layers of cortex are evident; and, microscopically, the middle reticular zone is considerably thicker than the outer glomerular-fascicular zones.

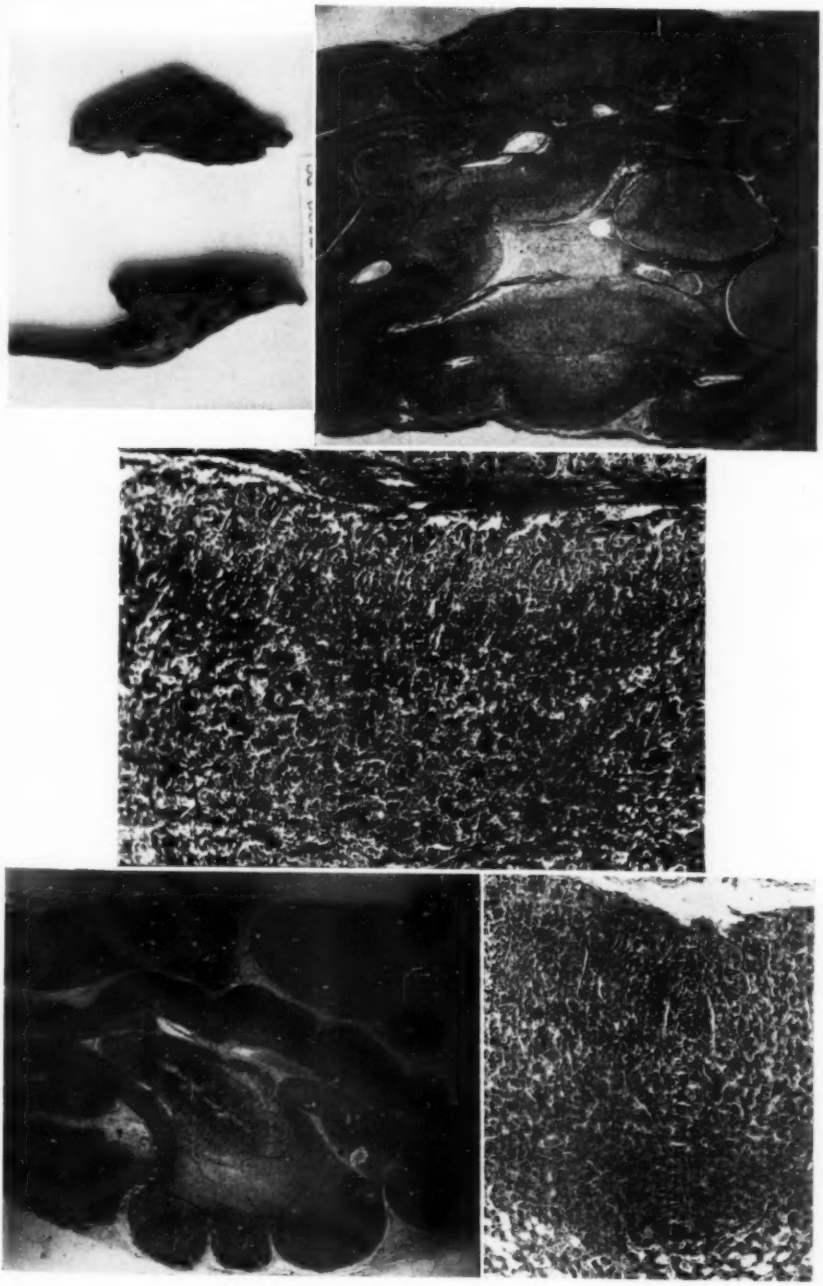

PLATE III

Case 5. Top: Enlarged, deeply pigmented, adrenal (left), and pigmented masses of aberrant adrenal in the testes (right).

Bottom: Oil immersion picture (left) to show pigment granules in the cells, and lower magnification (right) showing adrenal cortex composed altogether of reticular zone cells.

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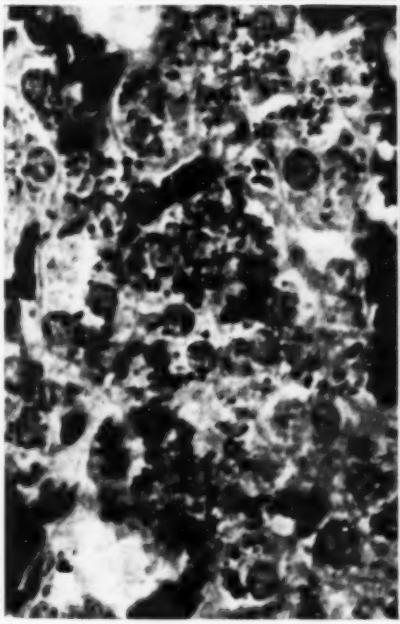


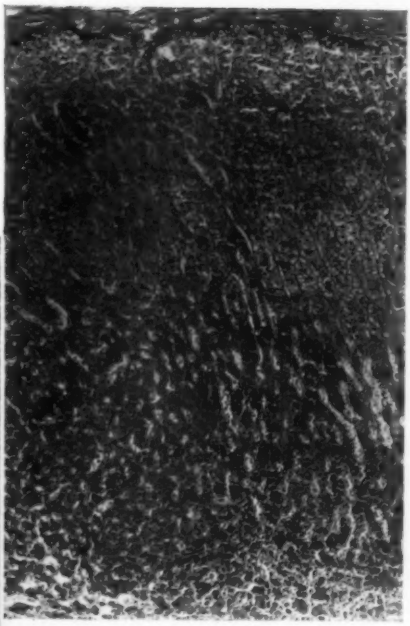
PLATE IV

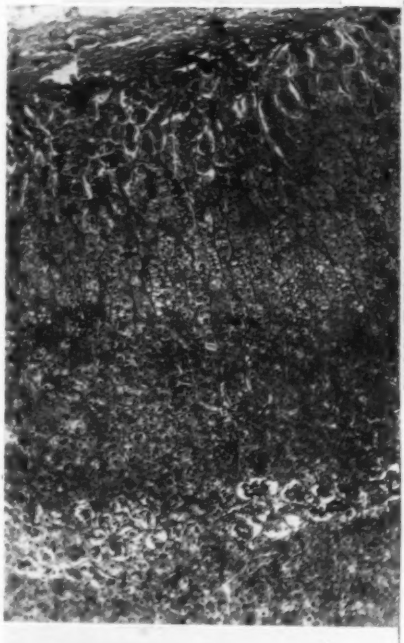
Left Top: Gross adrenal (in paraffin block) of Case 6, showing thick pigmented reticular zone.

Left Middle: Case 8. The reticular zone is nearly as thick as the outer glomerular-fascicular zones together and the cells stain more deeply.

Left Bottom: Case 9. Gross adrenals showing thick, irregularly pigmented, reticular zones.

Top Right: Case 7. The reticular zone of more darkly stained cells is as thick as the outer two zones together.





UNIV. OF MICH.

CEREBRAL INVOLVEMENT IN SCHISTOSOMIASIS JAPONICA

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Isolated reports of schistosomiasis japonica involving the central nervous system have appeared since 1906. In that year Tsunada and Shimamura (1) described a case with Jacksonian convulsions and a right hemiplegia. Nieva (2) in 1935 wrote of a case with convulsions which improved under therapy. In 1936 Egan (3) reported two neurological cases in a series of twelve English sailors who went swimming in the Yangtze river near Chinkiang. One year later Greenfield (4) described two cases explored for brain tumors and found to have schistosomiasis. Vitug and Cruz (5) in 1940 told of two Filipinos with cerebral schistosomiasis, one of whom was autopsied. These eight cases constitute the literature on neurological lesions in schistosomiasis japonica.

The present report includes five cases, all occurring on the island of Leyte in American troops in good health without previous exposure to this illness. In all except one case, the neurological manifestations took place in the acute stage. All cases occurred within seven months of exposure.

1.[1] This 21 year old officer was swimming in a Schistosoma japonicum infested river about 12 times between 6 and 24 December. On 20 January he had a febrile onset of symptoms with hives, headache, stomach aches and cramps, with an evening cough. On admission on 3 February he appeared lethargic, with a stiff neck and palpable glands in the posterior cervical chain. The liver was felt one finger breadth below the costal margin. The neurological examination was normal. He ran a moderately high fever for the first 4 days, following which it stayed around 100° until it returned to normal on the twelfth hospital day. On 6 February the stool was positive for mature ova of Schistosoma japonicum, and he was started on Fuadin. On the following day he appeared listless, and, in the afternoon, he had tonic or clonic spasms of the arms and legs. The deep reflexes were hyperactive in all the extremities with bilateral Hoffman's and bilateral

[1]Previously reported from this hospital by Billings, Winkenwerder and Hunninen (6).

Babinski's. He was incontinent of urine and feces. The eyes tended to deviate to the left, and a definite grasp reflex was present. The following day he became intermittently disoriented and remained so for 9 days. He reacted violently to any unpleasant stimuli. If he did not like the food he would spit it out. He was loud and noisy at times and would curse and swear. At other times he was drowsy and would sing and whistle to himself. Lumbar puncture on 8 February showed no cells and a negative Pandy. The leukocytes were 20,000 with 80 per cent eosinophiles. Treatment with Fuadin had been started on 6 February and was given every other day, the total of 40 cc. being finished on 23 February. Because this treatment was thought to be too slow in view of the severe symptoms, 20 mgm. of tartar emetic were administered intravenously on 7 February. His physical status remained the same until marked improvement began on 16 February. He became continent of urine and feces; his temperature returned to normal, and he began to take an interest in his surroundings. Weakness with signs of upper motor neurone involvement persisted in the right arm and leg. His neurological status improved only slightly until he was returned to the United States on 11 April.

This patient was the earliest and most severe case seen in this series. He was intermittently disoriented for a period of nine days, associated with incontinence of urine and feces. There was transient upper motor neurone involvement on the left with persistence of the same on the right until discharged. There was improvement concomitant with treatment and fall in temperature.

2. This 29 year old soldier came to the hospital on 19 January complaining of generalized aches and pains of 2 weeks duration. Early in November he swam about 12 times in a river since proved to be infested with cerceriae of Schistosoma japonicum. On 7 January he developed aches and pains over the body following a hard day's work on a bulldozer. These symptoms lasted for 3 days and were followed by generalized weakness, lassitude and upper abdominal discomfort. There had been no fever, neck stiffness, cough, or hives.

On admission on 19 January, he did not appear acutely ill. The liver and spleen were not palpable. There was no fever. The leukocytes were 33,200 with 78 per cent eosinophiles. The urine was

negative for bile. Two stools were negative. Repeated leukocyte count was 32,600 with 62 per cent eosinophiles. He ran a nightly fever to 100° for the first five days. Thereafter he was afebrile. Jaundice developed several days following admission and persisted until 12 February. On 30 January the liver was tender and just palpable. The tip of the spleen could just be felt. On 9 February he began to act peculiarly. He did not respond quickly to questions. On several occasions, he tore and ate pieces of paper. He ate his meals with his bare hands. On the following day he was transferred to the psychiatric service for further study of his abnormal behavior. When seen there, he was apathetic and lacked spontaneity. He was correctly oriented, but could not do calculations. Later that day he became disoriented as to time, place and person.

The general physical examination on 10 February was normal. Neurological examination showed intact cranial nerves. The deep and superficial reflexes on the two sides were equal and active. There was generalized muscular weakness, and he was unable to walk. The Babinski, Chaddock, Oppenheim and Gordon reflexes were present on both sides. There was no clonus. Sensory examination was normal. For the first time urinary incontinence was noted. A diagnosis of cerebral Schistosomiasis was made on the basis of the history of exposure and the clinical findings, and he was given 5 cc. of Fuadin intramuscularly. On the following day, 11 February, he was started on intravenous tartar emetic on alternate days until he had received 1.89 grams intravenously in 18 doses. The stool was positive for mature ova of Schistosoma japonicum on 18 February.

On 14 February the Babinski disappeared on the right, and he gradually gained control of urination. The mood steadily improved and spontaneity returned slowly. The Babinski remained present on the left until 22 February. Several days thereafter he began to walk. The gait remained slightly unsteady for several weeks. On 18 March he was reexamined on the psychiatric service. He was normally alert and spontaneous. Serial 7's were done correctly in one minute. Recent and remote memory were intact. There was no significant impairment in mental functioning.

On 13 May the stool was again positive for mature ova of Schistosoma japonicum. He had remained asymptomatic. The next day

sigmoidoscopy revealed many nodules typical of Schistosomiasis japonica. He was treated with 40 cc. of Fuadin in 8 doses given daily. Thereafter he was discharged and worked well and felt fine. Sigmoidoscopy on 19 July and again 15 August showed nodules typical of Schistosomiasis japonica. For this reason he was brought into the hospital and retreated with 60 cc. of Fuadin in 5 cc. daily doses, finished 29 August. Complete physical and neurological examinations at this time were normal, leukocytes were 10,850 with 18 per cent eosinophiles. Hematocrit was 50 per cent and sedimentation rate was 8 mm/hr.

This case was followed for 5 months after his first treatment. His symptoms disappeared during treatment and did not return. He was able to carry on his work very well. Nodules were present in the lower bowel from one month after treatment until five months thereafter. For this reason he was retreated at the end of five months.

3. A 20 year old soldier came to the hospital on 27 April 1945 complaining of loss of appetite of 7 days duration. During November 1944 he had worked in the swamps of an area now known to be infested with Schistosoma japonicum. The onset of symptoms occurred on 20 April with headache, fever and chills. Dark urine was noted 3 days later and jaundice appeared a few days later. On admission the liver was felt down 2 finger breadths. His illness followed a typical epidemic hepatitis course until 5 May when he had chills and a fever. The following day the fever reached 104°. The malaria smear was negative. The leukocytes were 5,750. He was given Penicillin, 20,000 units every 3 hours for 2 days with no temperature response. On 8 May the leukocytes were 6,000 with 4 per cent eosinophiles. There was a generalized headache with slight rotary neck stiffness. The liver was down 4 finger breadths below the costal margin. The neurological examination was normal. The presence of the high fever, enlarged liver and jaundice, with a normal white blood count suggested the diagnosis of amoebic hepatitis, and he was given carbosone and emetine. This diagnosis was given further support on the following day by the finding of cysts of Endamoeba histolytica in the stool. Trophozoites of Endamoeba histolytica were found on 15 May, but thereafter the stools were negative for amoebae. The blood culture and chest plate were normal. On 11 May massive

angioneurotic edema of the hands appeared associated with hives over the arms. The stools were negative for Schistosoma japonicum until 18 May when mature ova were found. The day after the positive stool he was started on Fuadin 5 cc. for 12 doses.

On 24 May he first noted weakness of the left arm. All the muscles were involved. There was no reflex or sensory change. The cranial nerves were intact. Three days later the arm was almost completely paralyzed. There was a Hoffman on the left. Mild weakness of the right arm developed with a transient Hoffman. A left facial weakness of the central type appeared at this time. There was slight disorientation. Lumbar puncture revealed no cells, and the total protein was 45 mgm. per cent. By the 31 May the strength in the left arm had begun to return; the left facial weakness and the right Hoffman had gone. The right arm was completely normal. The left biceps reflex was diminished and the abdominal and scrotal reflexes were absent. The liver and spleen were not felt. The temperature, which had been rising each afternoon, but gradually coming down, returned to normal on 31 May and remained there. The icteric index was 8 units.

Examination on 20 June showed that the fine movements of the left hand were well performed. The left Hoffman remained. The biceps and triceps reflexes were exaggerated in the left arm. On 2 July there was slight weakness of extension of the 4th and 5th fingers of the left hand. The left triceps and biceps were still accentuated and the left Hoffman persisted. The gait was normal.

The diagnosis of Schistosomiasis japonica here was not suggested until the outbreak of the hives and angioneurotic edema. The absence of eosinophilia and the presence of trophozoites of E. histolytica with jaundice seemed sufficient to explain the symptoms and course of the disease up to the time of the hives. On 9 June there was a leukocytosis of 12,550 with 16 per cent eosinophilia, but this was the highest value that these tests reached. The temperature chart was "saw-tooth" in character with a rise in the evening and a return to normal in the morning.

4. This 21 year old Corporal was camped in the swamps of a Schistosoma japonicum infested area between 1 March and 1 April, but could remember no direct exposure to fresh river water. On about 5 May

he developed malaise and fever to 102° in the afternoon. Four days later he had a cough productive of whitish phlegm. On admission on 11 May, the temperature was 103.2° with a pulse of 100. He appeared moderately acutely ill and was listless. He was quiet and somewhat suspicious and had an expressionless face. There was no general glandular enlargement. Fine moist rales were heard in the left lower chest and axilla with slight impairment of resonance in the same area. The liver and spleen were not felt. The neurological examination on admission was normal. The leukocyte count was 22,050 with 38 per cent eosinophiles. The fever continued to rise in the afternoon up to 103° for the first three weeks when it came to normal and remained there. Because of the productive cough, with fever and chest findings, a diagnosis of pneumonia was made, and he was started on Penicillin and given 380,000 units in the first 3 days. A chest X-ray was normal on the third day, and Penicillin was discontinued. There was no response of the fever to Penicillin. On 14 May he was still drowsy and listless. Marked weakness of the left arm with urinary incontinence appeared on this day. No sensory or reflex changes were present. The sudden onset of the weakness of the arm and incontinence, with a previous history of cough, fever, and eosinophilia strongly pointed toward a diagnosis of cerebral Schistosomiasis. Fuadin was started on the next day, and he was given 5 cc. daily for 12 days. On 16 May the lumbar puncture showed no cells and a total protein of 30 mgm. per cent. On 17 May there was clonus at the right ankle and patella. A Hoffman was present on the left. The stool was positive for mature ova of Schistosoma japonicum for the first time on this day. Six days later strength in the arm had improved. Giant urticaria appeared, spread generally over the extremities on this day and remained for 3 days.

On 4 June, 20 days after Fuadin was started and one month after the onset of the illness, he developed dyspnea and cyanosis. The pulse was 120; the cardiac apex beat was observed 3 cm. outside the nipple line; the second pulmonic sound was louder than the second aortic; systolic and diastolic murmurs were heard at the apex only; the percussion note at the left base was dull and the breath sounds were impaired; the liver was palpable 4 finger breadths below the costal margin; the spleen was down 1 finger breadth. He was digitalized. The chest plate on the following day showed increased

density at the right costo-phrenic angle. There were granular shadows in the upper lung fields. The heart shadow was enlarged to the right and left. In the next 5 days the signs of heart failure cleared, but the heart remained enlarged by X-ray until he was discharged to the U. S. A. on 25 July. At this time the neurological examination was normal except for weakness of the left grip.

In addition to neurological involvement in this case, there was the episode of sudden cardiac failure. At the time it was thought to be an attack of rheumatic fever. Among Egan's cases, however, there is one with a picture similar to this, and the possibility of this being part of Schistosomiasis japonica or a reaction to Fuadin remains open.

5. This 26 year old soldier in an engineering company was exposed on one occasion only to a Schistosoma japonicum infested stream in November of 1944. He felt well until 14 January 1945 when he had mild upper abdominal discomfort and a stiff neck. He was found to have an eosinophilia of 50 per cent and was hospitalized.

On admission on 29 January there was no fever and physical examination was normal. The leukocyte count was 8,250 with 13 per cent eosinophilia. Fourteen negative stools were followed by one showing immature ova of Schistosoma japonicum on 23 February. The patient was treated with Fuadin on alternate days to a total of 40 cc. in 9 doses, finished on 13 March. Thereafter, he felt well and was able to do light labor around the hospital. On 16 May immature eggs of Schistosoma japonicum were again isolated from the stool.

On 17 May while resting in bed, he experienced paresthesias of the left foot followed by a left-sided clonic convulsion. This lasted 5 minutes without loss of consciousness or incontinence. A second episode followed 5 hours later. On 20 May the physical examination was normal. Three days later he had a left-sided Jacksonian convulsion. It was presaged by an unpleasant sensation in the left foot and consisted of clonic and tonic spasms of the left leg and left arm. There was stertorous breathing, cyanosis, and unconsciousness. No incontinence occurred. The attack lasted about 10 minutes. One hour later there was a recurrence. Lumbar puncture and neurological examination were normal.

On 24 May left-sided weakness with some loss of position sense developed and progressed insidiously until about 12 June when left-sided hemiplegia was nearly complete. Reduced position sense

was present in the left leg and the left arm. There was numbness of the left upper lip and of the 3rd, 4th and 5th fingers of the right hand. The hemiplegia had progressed despite 60 cc. of intramuscular Fuadin in 5 cc. daily doses between 29 May and 9 June. Convulsions did not occur after 31 May. Skull plates and visual fields were normal. The leukocyte count was 7,750 with 3 per cent eosinophiles.

Because of progression of the neurological signs despite specific Schistosomiasis treatment, some doubt was thrown on the original diagnosis of cerebral Schistosomiasis, and a neoplasm was suspected. A right craniotomy was performed on 15 June by Lt. Col. August F. Jonas. Exploration of the motor area revealed no abnormality. Ventriculography on 29 June was normal. The left hemiplegia persisted after operation and the patient was evacuated to the U. S. A. on 5 July for further study.

This patient was exposed on only one occasion. The presence of a history of exposure, a stiff neck, a high eosinophile count together with immature ova in the stools is enough to make the diagnosis certain. A brain neoplasm as the cause of the neurological findings is unlikely in the light of a normal exploratory craniotomy and normal ventriculograms.

DISCUSSION

A search of the literature yields only 8 cases of symptomatic cerebral involvement in Schistosomiasis japonica. Four of these cases are proven pathologically, 2 by autopsy and 2 by operation. Two occurred early in the disease and 6 occurred late. In all of our cases ova of Schistosoma japonicum were found in the stools; there was a history of exposure, and there were clinical symptoms and laboratory evidence suggestive of Schistosomiasis japonica. All cases showed evidence of involvement of the pyramidal tract. All showed signs of cerebral involvement manifested by confusion, stupor or personality changes. The last case had irritative cerebral phenomena.

1. *Cerebral involvement in acute Schistosomiasis japonica*

The cases divide themselves clinically into 2 distinct symptom groups. In the first group there are 2 cases from the literature and 4 from our series. They had the onset of paralysis during the acute

stage of the disease within the first 6 months of exposure. There was drowsiness, usually followed by coma and incontinence. There were signs of pyramidal tract involvement with weakness, spasticity, exaggerated deep reflexes and usually Hoffman or Babinski. There was generally a high eosinophilia. As a rule the neurological signs started to improve when the temperature reached normal. Complete disappearance of neurological signs was unusual in the short period that these cases were observed here.

A. *Cases from the literature:* The 2 early cases from the literature are both from Egan's series. These occurred in a group of British sailors who swam near the mouth of an infested river while their ship was at anchor. The first sailor had a sudden onset 5 weeks after exposure with fever of 101°, epigastric pain and cough. A diagnosis of bronchitis was made. The following day paralysis appeared in both upper extremities. The tendon jerks were exaggerated in all extremities, and the Babinski was present on both sides. The eosinophile count was 52 per cent. Drowsiness and listlessness increased, and he became comatose with incontinence and remained so for 10 days. Treatment was with tartar emetic. At the end of 6 months strength and mental functioning were normal.

The second sailor was exposed at the same time and in the same place. He had a sudden onset at the end of 5 weeks with intense headache, abdominal pain, and a temperature of 103°. For one week he was drowsy and listless. Then he lapsed into coma which lasted for about 8 days, during which a left-sided hemiplegia developed gradually. He was restless, screaming and shouting most of the time. A full course of Fuadin was given with improvement. Tendon reflexes slowly returned to normal, but the paralysis never completely cleared.

B. *Cases from our series:* Into this group go the first 4 cases of this series. All had the onset of their neurological symptoms within 6 months of exposure. The second case had a mild febrile reaction lasting for only 5 days. He was afebrile for 16 days before the onset of his neurological symptoms. The other patients ran a high fever. All showed definite improvement in their mental and neurological functions within 2 days of the return of the temperature to normal. All patients showed disorientation during the height of their neuro-

logical disorder. The first patient was partially disoriented for 9 days during which time he sang and whistled to himself, spit food out if he did not like it, cursed and screamed. He was incontinent of urine and feces during this period. The other patients showed mild degrees of disorientation lasting for only a day. The third patient, who was the least disoriented, was not incontinent. Incontinence lasted for 16 days in case No. 1, for 4 days in No. 2, and 1 day in No. 4.

Signs of pyramidal tract involvement were present in all cases.

TABLE 1

Incidence of characteristic neurological signs or symptoms in 6 cases of acute cerebral schistosomiasis japonica

SIGN OR SYMPTOM	INCIDENCE		PERCENTAGE OCCURRENCE OF EACH SYMPTOM	
Fever	6 patients		100	
Disorientation	5 patients		83	
Incontinence	4 patients		67	
	left	*right*	*left*	*right*
Paralysis				
Arm	5	2	83	33
Leg	3	2	50	33
Facial nerve	2	0	33	0
Hyperactive reflexes				
Biceps	4	2	67	33
Triceps	4	2	67	33
Knee jerk	3	2	50	33
Ankle jerk	3	2	50	33
Hoffman	3	2	50	33
Babinski	3	2	50	33
Grasp reflex	1	1	17	17

Every case had a sudden onset of weakness, and maximum involvement was complete within several hours. In No. 1 all reflexes became hyperactive with bilateral Hoffman, bilateral Babinski and ankle clonus. A definite grasp reflex was present. At the time of transfer to the United States all the reflexes were still hyperactive. Only the left Hoffman had disappeared. In No. 2 the tendon reflexes were normal. A Babinski was present bilaterally. The one on the right disappeared after several days, whereas the left one persisted for 3

weeks. No. 3 had weakness in the left arm developing over a 3 day period. There was diminution in the biceps reflex and a Hoffman was present on that side. At this time a transient weakness of the right arm occurred with a Hoffman, lasting for one day. On discharge to the United States, the left biceps and triceps reflexes were hyperactive and a Hoffman was still present. This was the only case in which there was a disturbance of the cranial nerves. The facial weakness was thought to be central in origin. In No. 4 weakness associated with a positive Hoffman and accentuated triceps and biceps reflexes developed and remained constant.

Lumbar punctures were done in Nos. 1, 3 and 4 at the height of the neurological involvement and in all cases were normal. In Nos. 1 and 3 the diagnosis was made from a positive stool examination and treatment was started before neurological symptoms appeared. Nos. 2 and 4 were started on treatment before the stool was positive because of the severity of the neurological symptoms. Nos. 1, 3 and 4 were treated with Fuadin, while No. 2 had tartar emetic. Improvement followed treatment dramatically in No. 1, to a lesser degree in Nos. 2 and 4. In No. 3 the neurological symptoms developed after Fuadin had been given in 5 cc. daily doses for 5 days. At the onset of the fever in No. 1 the leukocytes were 20,000 with 80 per cent eosinophiles, in No. 2 they were 32,600 with 62 per cent eosinophiles, in No. 3 they were 6,000 with 4 per cent eosinophiles, and in No. 4 they were 22,500 with 38 per cent eosinophiles. The fact that the leukocytes and the eosinophiles were normal in No. 3 delayed the diagnosis and treatment.

2. *Cerebral involvement in chronic Schistosomiasis japonica*

A. *Cases from the literature:* The second group is characterized by epileptic attacks which are not reported in the literature in the acute stage of the illness. Several have been mistaken for brain neoplasms and subjected to operation. There are 6 cases from the literature. Tsunada and Shimamura reported an autopsy on a Japanese builder, 32 years of age. He gave a history of abdominal pain and indigestion in 1901. In 1903 he had convulsive seizures with loss of consciousness, followed by aphasia. He had headaches and was drowsy. In November of 1903 he had right Jacksonian fits 2 or 3 times a day

followed by right hemiplegia. He died in August of 1904. The autopsy was normal except for the brain and its coverings. The cerebral meninges showed diffuse thickening. There were small tubercles in the left parietal region, involving both the white and gray matter. A large area of softening was present involving the internal capsule, the optic thalmus and the right hemisphere. The microscopic appearance of these lesions is not described other than that they revealed ova of Schistosoma japonicum.

TABLE 2

Incidence of characteristic neurological signs or symptoms in 7 cases of chronic cerebral schistosomiasis japonica

SIGN OR SYMPTOM	INCIDENCE		PERCENTAGE OCCURRENCE OF EACH SYMPTOM	
Epileptic attack	6 patients		86	
Unconsciousness	4 patients		57	
Paresthesias	4 patients		57	
Headaches	3 patients		43	
Hemiplegia	3 patients		43	
Visual field defects	2 patients		29	
Hemianesthesia	1 patient		14	
	left	*right*	*left*	*right*
Paralysis				
Arm	0	2	0	29
Leg	1	0	14	0
Hyperactive reflexes				
Biceps	0	1	0	14
Triceps	0	1	0	14

Two cases are reported by Greenfield. Both came to exploratory craniotomy for brain tumor and were found to have schistosomiasis japonica when the sections were examined microscopically. The first man had a series of attacks starting in December of 1935, ushered in by an unpleasant sensation in the legs, associated with obscuring of peripheral vision and climaxed by unconsciousness. Physical examination showed mental slowing with pinkness of the optic discs and a right homonomous hemianopsia. There was "some eosinophilia." Lumbar puncture revealed a pressure of 200 mm. of water, a protein of 22 mgm. per cent, and 72 cells, of which 93 per cent were

lymphocytes. Exploration on 20 January of the left parietal-occipital region uncovered a friable yellow mass which was removed. On microscopic examination, ova of Schistosoma japonicum were found in it. On questioning, the patient gave a history of being in an endemic area for this disease in China 4 years previously. He was treated with 30 grains of tartar emetic from 6 February to 6 March. In 6 months he appeared well.

The second man had the onset with a headache three days after he hit his head while playing cricket on 4 July. This lasted for 7 days. One month later he was seen by a doctor who obtained a history of mild weakness of the right arm and right leg beginning in May. A right lower quadrant hemianopsia was present. A subtemporal decompression was performed on 11 August, followed in 4 days by a left occipital lobe exploration, with no abnormal findings. One month later, the visual defect had increased. There was intense papilledema with hemorrhages and exudates. The right arm was weak with brisk reflexes. He was again subjected to craniotomy, and a mass was removed from the upper part of the right occipito-parietal region. On section ova of Schistosoma japonicum were found. Recovery was nearly complete several months after operation.

Three cases have been reported from the Philippines. In 1935 Nieva saw a man from Samar who was having convulsions, dizziness, numbness and headaches. His stool was found to contain ova of Schistosoma japonicum. He was treated with tartar emetic and emetine hydrochloride. He improved on this therapy. Because he had positive stools and improved on treatment, he was believed to have schistosomiasis japonica. No further proof of the diagnosis is available. Five years later Virtug and Bautista report 2 more cases in Filipinos with one autopsy. Both came from Samar. A 20 year old male entered the hospital following a series of convulsive seizures. Four months prior to admission he had an isolated fit presumably similar to the ones witnessed at the hospital. The attacks started with tremors first in the upper limbs and then in the lower. The eyeballs rolled upward, and the body assumed the opisthotonic position. Following hospitalization he remained comatose for 4 days. During the first 3 days of hospitalization fits occurred irregularly and frequently and lasted from 5 to 45 seconds. On the eighth day he

developed paresis of the left lower and right upper extremity. There was difficulty with speech. He also ran an intermittent moderately high fever. There were no abnormal reflexes. The leukocyte count ranged between 17,700 and 10,850 with 1 per cent eosinophiles. He died in a convulsive attack on the eleventh day. The autopsy showed cirrhosis of the liver and shallow ulcers of the colon. Smears from the liver and colon surfaces revealed many ova of Schistosoma japonicum. The pia-arachnoid appeared rough and granular over the posterior third of the left superior frontal convolution, the left hippocampal gyrus, uncus and the right orbital gyrus. On sectioning these areas, increased resistance was encountered. The cortex and the underlying white matter appeared rough and indurated with distinct whitish pin-point-sized tubercles. Microscopic examination of these areas showed encapsulated ova, single and in nests. These had macrophages, round cells and occasional multinucleated giant cells around them. The capillaries of the choroid plexus of the left lateral ventricle were plugged with ova of Schistosoma japonicum. A few eggs were found in the lung. The liver also contained ova surrounded by macrophages and round cells.

The second patient was 40 years old and had a history going back for one year. At that time he experienced a gradual onset of numbness over the right side of the body. Somewhat later, weakness developed on the same side. Suddenly, on the day before admission, he had tremors and spasmodic contractures of the right upper and lower limbs followed by paresis on the same side. On physical examination there was right hemiparesis and hemianesthesia to pain, touch and temperature. During the first week he had daily attacks of spasms of the muscles on the right side of the body. The stool was positive for Schistosoma japonicum. He was treated with 2 courses of Fuadin. Gradually strength and sensibility returned on the right side. He was discharged well after 2 months. The leukocyte count was 7,550 with 2 per cent eosinophiles. Three lumbar punctures were normal. The stool was also positive for hookworm, ascaris and trichuris trichiura.

B. *Case from our series:* Into this group falls the last of our cases. He is the only one seen here with neurological symptoms starting 6 months after exposure. The onset was dramatic with a Jacksonian

convulsion on the left. This was followed by the development of a left hemiplegia. The leukocyte count and eosinophile count were normal. There was no improvement with therapy.

Pathology

There is good reason to believe that the pathological lesions in early schistosomiasis are different from those found late in the chronic stage. No autopsies have been reported on early cases of cerebral schistosomiasis. Two late cases have come to autopsy and two have been operated on. In the late cases macroscopic tubercules and large granulomatous areas were found containing grouped ova of Schistosoma japonicum surrounded by scarring and foreign body reaction. In some cases the scarring interrupted the blood supply to various parts of the brain and caused softening in such areas. In cases autopsied the ova were not found spread uniformally throughout the brain and other organs, but were localized into tubercules and granulomas. This fact throws some doubt on the theory that the ova are produced in the mesenteric veins and the liver and disseminated through devious channels to the brain. The localized nature of the process at autopsy suggests a local origin of the ova. So far, however, no worms have been found in the brain substance.

The patients having cerebral involvement during the acute stage of schistosomiasis japonica have tended to show more improvement with treatment than those developing cerebral symptoms late in the disease. This fact suggests that there is a less permanent type of underlying lesion in the early cases. Faust and Meleney (7) working with experimentally infected laboratory animals, have described small hemorrhages occurring around the young worms in all organs except the liver, shortly after exposure. They have also noted chronic passive congestion of all the viscera in a rabbit killed on the ninth day following infection. Such lesions are reversible and could explain the return of function found in the acute cases.

SUMMARY

Five cases of cerebral involvement in schistosomiasis japonica are reported from the schistosomiasis epidemic which occurred among American troops on Leyte, P. I. starting in the latter part of 1944.

Four of the reported cases showed neurological involvement in the acute stage of the disease, and one case showed neurological involvement 4 months after the acute stage. Those occurring in the early stage showed acute onset of drowsiness followed by coma and incontinence. There were signs of pyramidal tract involvement with weakness, spasticity and exaggerated deep reflexes. There was moderate eosinophilia. Symptoms improved with therapy. Neurological involvement in the late stage was manifested by Jacksonian convulsions, followed by the development of a hemiplegia, but without drowsiness, coma or incontinence. Cases from the literature are reviewed and the pathology is discussed.

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CUTANEOUS DISTRIBUTION OF PERIPHERAL NERVES IN RHESUS MONKEYS AS DETERMINED BY THE ELECTRICAL SKIN RESISTANCE METHOD*

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Previous publications from this laboratory (9, 10, 11, 12) have demonstrated that the cutaneous distribution of sympathetic nerve fibers can be studied by the electrical skin resistance method. The technique is based on the principle that the resistance offered by normal skin to the passage of a minute direct current is related to the activity of sweat glands. Sweat gland activity is, in turn, a manifestation of the action of sudorific nerve fibers contained in the thoracolumbar outflow of the autonomic nervous system. Any depression or destruction of this sudorific nerve supply, either central or peripheral, increases the resistance of the area of skin supplied by the nerves whose function is depressed. The observations reported here concern the immediate and certain of the prolonged effects produced on the electrical resistance of the skin by transections of peripheral nerves in rhesus monkeys. Such peripheral nerve transections produce disturbances in sweating because postganglionic sympathetic nerve fibers are severed along with afferent and somatic efferent fibers.

Disturbances of sweat secretion following lesions of peripheral nerves have been observed and studied by various techniques. Observation of the degree of visible sweating is the simplest and most used method of studying sweat secretion. Langley (6, 7) used this method experimentally to record the location of droplets of sweat following stimulation of a peripheral nerve. These observations led Langley to conclude that there is a similarity between the cutaneous distribution of afferent and sympathetic nerve fibers. Sherrington (13) extended these obser-

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vations and formulated the hypothesis that postganglionic sympathetic fibers entering a spinal nerve through its gray ramus supply the same zone of skin served by the corresponding posterior root ganglion. Colorimetric methods of detecting and outlining areas of disturbed sweat secretion have received attention. Guttmann (2) has applied Minor's starch-iodine method and, more recently, the chinizarin method to the detecting and outlining of areas of disturbed sweat secretion in complete lesions of peripheral nerves. These methods have shown that the area of disturbed sweating corresponds in general to the area of altered sensibility. The loss of sweating is complete only within the autonomous zone of the peripheral nerve; hypohydrosis can be detected by these colorimetric methods in the mixed or intermediate zone of the nerve. Preliminary reports (5, 10) indicate that the electrical skin resistance method provides another means of study of disturbed sweat secretion in peripheral nerve lesions which is both simple and delicate.

METHODS

Rhesus monkeys (*Macaca mulatta*) were operated under ether anesthesia. A peripheral nerve in an extremity was exposed at a selected level, transected, and sutured. Rotation of the cut ends at the time of suture was minimized by the placing of sutures in corresponding surfaces of the nerve proximal and distal to the level of proposed transection before the cut was made. After the transection, the cut ends were sutured with 6-0 black silk swedged onto fine round needles. Connective tissues and skin were sutured with heavier black silk. No dressings were placed over the incisions. Skin sutures were removed about the fifth postoperative day. A total of 55 peripheral nerves were so severed and sutured in 10 animals.

The skin was tested at frequent intervals for areas of elevated skin resistance following recovery of an animal from the anesthesia. When an area of high resistance was found, its borders were marked with a wax skin-pencil. Record of the border was made by 1) drawing the zone on a standardized printed outline of the extremity,[2] 2) writing

[2] In these printed forms, which are essentially the same as those used for human subjects, there are no blind areas. Thus every part of the surface of the arms or legs is shown on one or the other of the charts. (1945: Richter, Curt P., and Malone, P. D., Peripheral Nerve Lesion Charts. J. Neurosurg., vol 2, no. 6, pp. 550–552.)

descriptions in the protocols, and 3) taking photographs of the extremity with the skin marks present. In many specimens the borders were tattooed with India ink to facilitate the recognition of alterations in the skin resistance patterns.

The instrument used in detecting the areas of altered resistance is a modification of the one described in detail elsewhere (12, 15). Its essential parts are: a microammeter, four $4\frac{1}{2}$-volt batteries, a 1000-ohm potential divider, and electrodes. The modification consists in the addition of three $4\frac{1}{2}$-volt batteries to the one $4\frac{1}{2}$-volt battery contained in the standard apparatus. A switch is provided so that $4\frac{1}{2}$, 9, $13\frac{1}{2}$, or 18 volts can be thrown into the circuit at will. A smooth increase of current from 0 to 18 volts is obtained by the combined use of the switch and potential divider. The amount of current flowing in the circuit at any given time depends upon the resistance of the skin. The general rule followed in this study was that a sufficient potential to cause a current of 15 to 20 microamperes is placed in the circuit. Thus gradations of increases in resistance can be detected by decrease in current through adjusting the current to give nearly full-scale deflection of the microammeter needle in areas of low resistance. When searching a region suspected of having an elevated resistance, the corresponding normal area is tested first and the instrument adjusted so that the needle of the microammeter is deflected 15 to 20 microamperes each time the skin is touched with the movable electrode. The denervated area is then explored with the movable electrode. If no current flows, the area is described as having a *high resistance*; if some current flows, but the amount is clearly less than the corresponding normal area, the region is considered to have an *intermediate resistance*.

The principal technical problem encountered in making skin resistance observations on monkeys is the production of adequate sweating. The animal must be sweating in order to lower the resistance of normally innervated skin sufficiently to permit detection of the high resistance of the denervated regions. Two methods of achieving sweating were tried: 1) application of external heat, and 2) administration of Furmethide (furfuryl-trimethyl-ammonium iodide), a parasympathetic-comimetic drug. The application of external heat was carried out by placing the animal under a surgical heat cradle containing a total bulb wattage of 440. Adequate sweating was detected by testing frequently

the resistance of normally innervated skin until satisfactory lowering occurred. The application of heat was continued throughout the examination because a fall in body temperature produces an immediate cessation of sweating even with internal body temperature higher than normal. Excessive application of heat was avoided also by reducing the amount in order to prevent direct stimulation of denervated sweat glands by a marked local temperature rise.

Subcutaneous administration of 0.5 to 1 mg. of Furmethide produces a profound sweating response in rhesus monkeys which reaches a maximum within 5 minutes or less. The amount of sweating so produced is adequate for skin resistance studies. There is a disadvantage to the use of Furmethide, however, which caused its abandonment in favor of external heat in this study. Comparison of the borders of areas of high resistance obtained first after heating and then after Furmethide shows that for the first 6 to 8 weeks following nerve transection the use of Furmethide lowers the resistance of the denervated area to such an extent that differences from adjacent normal areas are difficult to detect. Prolonged application of external heat produces a similar lowering of resistance in denervated areas but the effect is less pronounced and can be controlled by reducing the amount of heat. After 6 to 8 weeks postoperatively, borders obtained by external heat and Furmethide are usually identical but minor differences occur with sufficient frequency in rhesus monkeys to raise doubt concerning the accuracy of the skin resistance patterns obtained with the use of Furmethide.

Dissections of the cutaneous branches of nerves to the extremities were made on formalin-preserved material. The branches of the cutaneous nerves were followed as far as possible with the unaided eye to determine the general cutaneous area supplied by each peripheral nerve. Three to five dissections were made of each nerve. Composite drawings were then made of these dissections to show the most common location and arrangement of the larger cutaneous branches.

RESULTS

Areas of high skin resistance immediately following nerve transections

The areas of high electrical skin resistance found immediately after transections of peripheral nerves are described in the paragraphs which

follow. The accompanying drawings and photographs (Figs. 1, 2, 3, 5, 6) illustrate the observations made on selected nerves from the series.

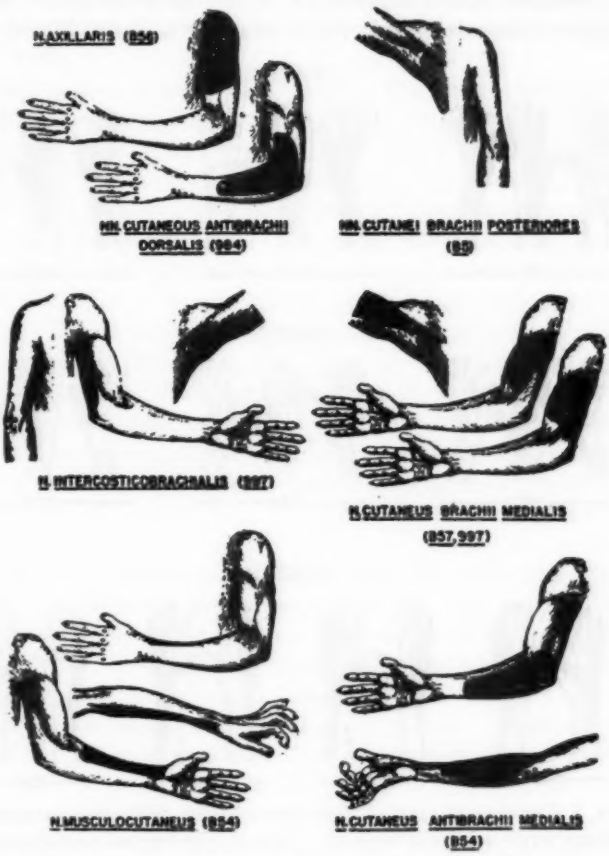

FIG. 1. Drawings of areas of high skin resistance produced by transection of peripheral nerves supplying the arm and forearm. Areas of high resistance are shown in solid black; numbers in parentheses are animal codes.

N. axillaris, cut in two specimens (B56, B61) at its origin from the posterior cord of the brachial plexus. High resistance is found over the deltoid region of the arm, extending distally below the site of insertion

of the deltoid muscle, proximally to the acromial process, and at its sides to the anterior and posterior surfaces of the arm (Figs. 1, 3—#5).

N. cutaneus brachii posterior, cut in one specimen (B5). The area of high resistance is located over the posterior axillary fold and extends

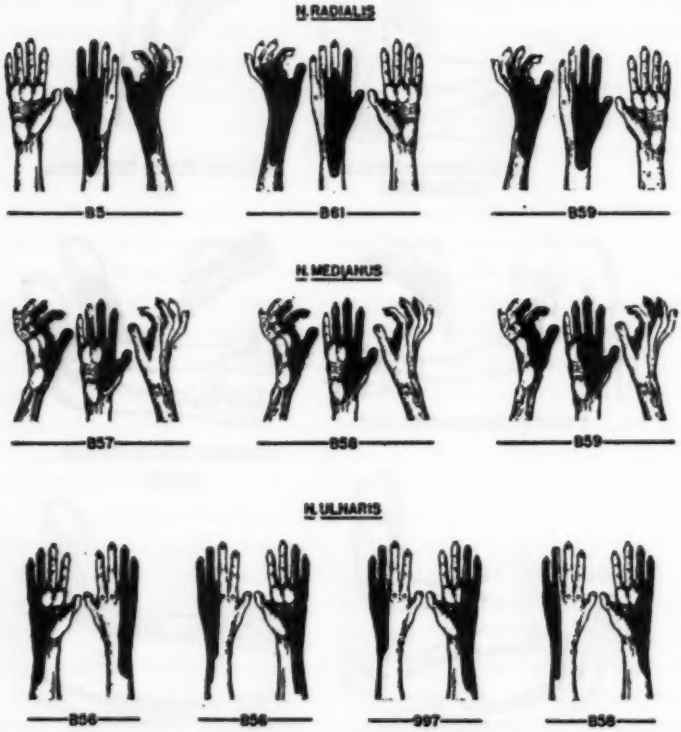

FIG. 2. Drawings of areas of high skin resistance produced by transection of peripheral nerves supplying the hand. Areas of high resistance are shown in solid black.

a short distance over the posteromedial aspect of the proximal region of the arm (Figs. 1, 3—#3 and 4).

N. cutaneus antibrachii dorsalis, cut separately in one specimen (984) and involved in two high radial nerve transections (B5, B61).

The zone of high resistance occupies the posterolateral surface of the distal one-third of the upper arm and continues over the posterior surface of the proximal two-thirds of the forearm, becoming continuous distally with the field of supply of the superficial radial nerve (Figs. 1, 3—# 10).

Ramus superficialis n. radialis, sectioned in three specimens (B61, 984, B59) in the midforearm. The most constant pattern of high resistance is one extending over the lateral half of the posterior surface of the distal one-third of the forearm and then continuing over the lateral dorsal surface of the hand. The medial extent of the hand area is a line projected proximally through the middle of digit IV. The hand pattern thus includes the dorsal surfaces of digits I, II, III and lateral half of IV. In some specimens the distal phalanges of digits III and IV are not involved in the area of high resistance. There is also variation in the degree of inclusion of the middle and proximal phalanges of digit IV in the pattern (Figs. 2, 3—# 14 and 15).

N. musculocutaneus, cut in two specimens (984, B54). A zone of high resistance starts on the forearm near the elbow and extends distally on the lateral half of the anterior surface as far as the base of the thumb where it joins the area supplied by the median nerve (Figs. 1, 3—# 8 and 9).

N. medianus, transected in six specimens (B57, B54, B58, 984, B45, B59) at various levels in the upper extremity. The maximal area of high resistance is located on the palmar surface of the hand (Figs. 2, 3—# 11). The area includes that portion of the palm which extends laterally from a line projected down the middle of digit IV and continues over the palmar surfaces of digits I, II, and III, and lateral portion of IV. The proximal limit of the pattern is the base of the thenar eminence. A common variant is exclusion of all or part of the third interdigital pad (B57, B58, in Fig. 2).

N. ulnaris, severed in six specimens (B45, B56, B54, B58, B57, 997). The pattern involves the distal one-third of the medial portions of the anterior and posterior surfaces of the forearm and extends over the corresponding areas on the hand (Fig. 2, 3—# 12 and 13). Imaginary lines projected down the middle of digit IV best demarcate the lateral borders of the anterior and posterior zones on the hand. The ulnar pattern often includes all the posterior surface of digit IV (B56, Fig.

FIG. 3. Photographs of areas of high skin resistance produced by transections of peripheral nerves to the upper extremity. Areas of high resistance are outlined by black lines. 1. *n. intercosticobrachialis*, 2. *n. cutaneus brachii medialis*, 3. Posterior view of *n. cutaneus brachii posterior*, 4. axillary view of *n. cutaneus brachii posterior*, 5. *n. axillaris*, 6. medial view of *n. cutaneus antibrachii medialis*, 7. posterior view of *n. cutaneus antibrachii medialis*, 8. anterior view of *n. musculocutaneus*, 9. posterior view of *n. musculocutaneus*, 10. *n. cutaneus antibrachii dorsalis*, 11. *n. medianus*, 12. anterior view of *n. ulnaris*, 13. posteromedial view of *n. ulnaris*, 14. posterior view of *n. radialis*, 15. lateral view of *n. radialis*.

2). The degree of involvement of the third interdigital pad varies from none in B56 to a partial inclusion on the pad in B58 and 997 (Fig. 2).

N. cutaneus brachii medialis, cut in two specimens (B57, 997). An area of high resistauce is found confined to the anterior half of the medial surface of the arm (Fig. 1, 3—# 2). The pattern starts proximally in the apex of the axilla and extends distally to terminate near the elbow. A peculiar extension of the pattern over the olecranon process was noted in 997 (Fig. 1).

N. cutaneus antibrachii medialis, transected in two specimens (B58, miscoded B54 in Fig. 1; B59). The zone of high resistance produced by sectioning this nerve occupies most of the antecubital fossa and then extends medially down the anteromedial surface of the forearm to the ulnar area at the start of the distal one-third of the forearm (Figs. 1, 3—# 6 and 7).

N. intercosticobrachialis, cut in two specimens (B54, 997). The area of high resistance extends over the posterior half of the medial surface of the arm from axilla to elbow (Figs. 1, 3—# 1). The zone includes all the posterior surface of the arm and a portion joins the lateral surface where it becomes continuous with the axillary, posterior brachial cutaneous, and posterior antibrachial cutaneous areas.

N. cutaneus femoris lateralis, severed in two specimens (B57, B45). A broad area of high skin resistance is found extending over the lateral aspect of the buttock and thigh, continuing distally as far as the inferior margin of the patella. The zone covers also the anterior surface of the thigh and a narrow strip extends over to the medial surface of the thigh (Figs. 5, 6—# 20 and 21).

N. femoris, cut at the inguinal ligament in two specimens (B5, 997); severed at the knee (saphenous nerve) in three specimens (997, 984, B45). The skin resistance pattern for the femoral nerve involves the medial surface of the lower extremity, extending from the inguinal ligament to the medial border of the sole of the foot (Figs. 5, 6—# 16 and 17). The medial half of the dorsal surface of the great toe is constantly the most distal extent of the femoral zone. The pattern for the saphenous nerve is identical with the leg and foot portions of the area just described for the femoral nerve (Figs. 5, 6—# 18 and 19).

N. cutaneus femoris posterior, severed in one specimen (B58). There

is a wedge-shaped area of high resistance located over the posterior aspect of the buttock and thigh (Figs. 5, 6—# 22). The broad portion of the wedge is based proximally on the ischial tuberosity; the tapering

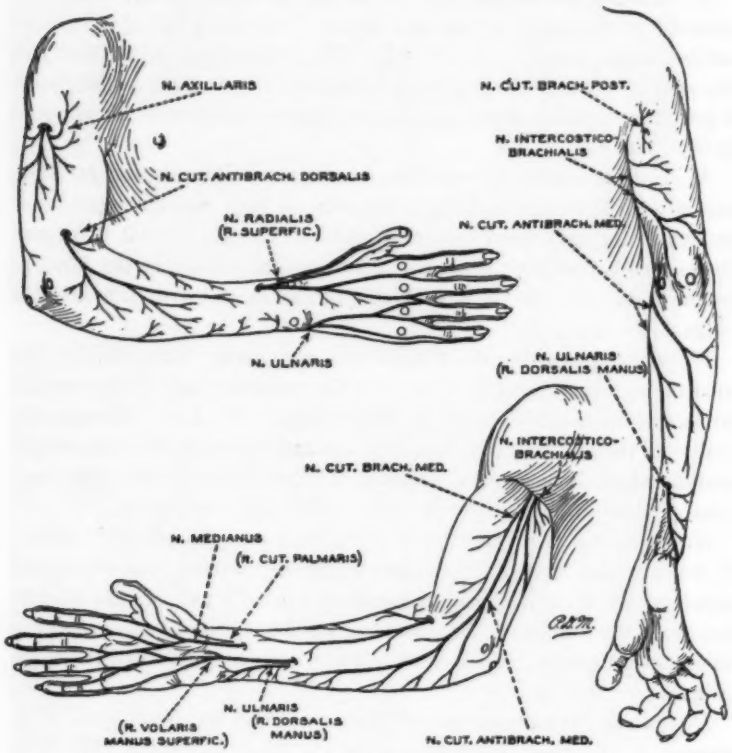

FIG. 4. Drawings of dissections showing cutaneous branches of nerves to the upper extremity of *Macaca mulatta*. The unlabelled nerve shown on the lateral surface of the forearm is *n. cutaneus antibrachii lateralis*.

portion continues distally over the posterior surface of buttock and thigh to a termination at the popliteal fossa.

N. ischiadicus, transected in three specimens at midthigh (B61, B59, B56). The pattern involves all the leg and foot except for the medial surfaces of these parts (Figs. 5, 6—# 23, 24 and 25). The lateral portion of the dorsal surface of the great toe marks the site of junction of

the distal border of the sciatic pattern with the area supplied by the femoral nerve.

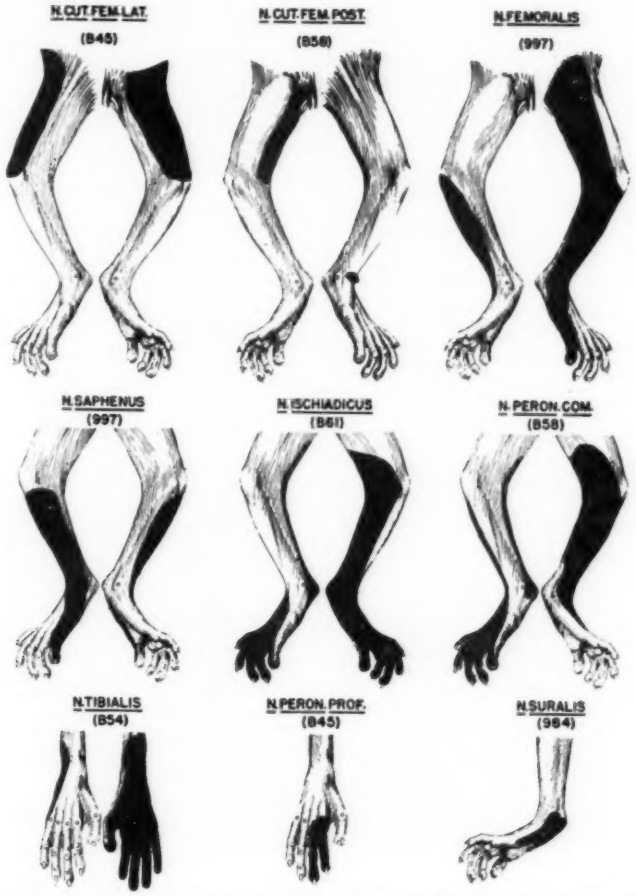

FIG. 5. Drawings of areas of high resistance produced by transection of peripheral nerves supplying the lower extremity. Solid black indicates areas of high resistance.

N. suralis, cut in two specimens (984, B57). An area of high resistance is found over the lateral malleolus with a narrow extension distally along the lateral margin of the foot (Figs. 5, 6—* 30).

FIG. 6. Photographs of areas of high skin resistance following transections of nerves to lower extremity. Areas of high resistance are outlined by black lines. 16. medial view of *n. femoris*, 17. anterior view of *n. femoris*, 18. medial view of *n. saphenus*, 19. anterior view of *n. saphenus*, 20. anteromedial view of *n. cutaneus femoris lateralis*, 21. lateral view of *n. cutaneus femoris lateralis*, 22. *n. cutaneus femoris posterior*, 23. medial view of *n. ischiadicus* 24. posterior view of *n. ischiadicus*, 25. lateral view of *n. ischiadicus*, 26. plantar view of *n. tibialis*, 27. lateral view of *n. tibialis*, 28. lateral view of *n. peroneus communis*, 29. anterior view of *n. peroneus communis*, 30. *n. suralis*.

N. peroneus communis, cut in two specimens (B57, B58). The pattern starts at the knee and extends over the lateral surface of the leg to the dorsal surface of the foot. The dorsal surfaces of all the toes are included in the pattern except for the medial portion of the dorsum of the great toe and a narrow strip along the lateral aspect of toe V (Figs. 5, 6—## 28 and 29).

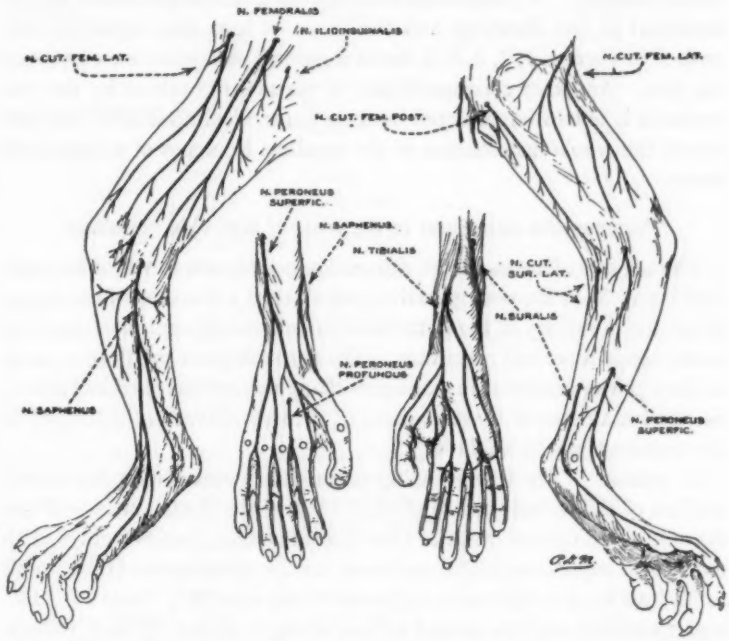

FIG. 7. Drawings of dissections showing cutaneous branches of nerves to the lower extremity of *Macaca mulatta*.

N. tibialis, severed in two specimens (B56, B54). The sole of the foot, the plantar surfaces of the toes except for a portion of the medial surface of the great toe and a narrow strip on the lateral surface of the dorsum of the foot show a high skin resistance (Figs. 5, 6—## 26 and 27).

N. peroneus profundus, cut on both sides in specimen B45. The area of high resistance is located on the dorsal surface of toes II and III,

extending from the prominence of the metatarsophalangeal articulations to the distal extremities of these toes (Fig. 5).

Anatomy of cutaneous branches of peripheral nerves to the extremities

The drawings (Figs. 4, 7) represent the most common locations of the larger branches of the cutaneous nerves of the extremities of the rhesus monkey. A comparison between the anatomical areas of supply indicated in the drawings and the zones of high skin resistance described in Figures 1, 2, 3, 5, 6 shows a general correspondence between the two. An exact correspondence of the areas obtained by the two methods is not to be expected because anatomical dissection does not reveal the whole distribution of the smallest branches of a cutaneous nerve.

Postoperative alterations in the areas of high skin resistance

The borders of areas of high skin resistance remain constant for variable intervals in the postoperative period, then a lowering of resistance about the periphery of the patterns commences and continues until the zones regain a normal resistance. The chronology of the time of onset of these postoperative skin resistance changes is summarized in Table 1. Selected examples of these changes in sutured nerves are described in the paragraphs which follow.

N. radialis. The first lowering of resistance occurs over the lateral portion of the dorsal surface of digit IV and the dorsal surface of the thumb. The time of onset of these initial changes varies from 8 to 16 days for a superficial radial sectioned in the midforearm (B59) to 32 to 38 days for a radial nerve sectioned in the arm (B5, Table 1). The high resistance over the dorsal surface of digits II and III next lowers. The subsequent changes consist in a gradual concentric shrinkage of the zone over the lateral portion of the dorsal surface of the hand. In one specimen the resistance returned to normal over the radial area in 103 days following transection and suture of the superficial radial nerve (B59).

N. medianus. The central palmar portion of the median area manifests a lowering of resistance within 4 days or less following transection of the median nerve. The level of the section appears not to be related to the time of onset of these first changes in palmar resistance. This

TABLE 1

Period of onset of changes in skin resistance observed in a selected group of peripheral nerves following section and suture

NERVE SECTIONED	ANIMAL CODE	LEVEL OF SECTION AND SUTURE	PERIOD OF ONSET OF FIRST CHANGES IN SKIN RESISTANCE
			days
n. axillaris	B56	Axilla	57–64
n. radialis	B5	Midarm	32–38
	B61 (L)	Axilla	27–43
	B61 (R)	Midforearm	17–23
	B59	Midforearm	8–16
n. musculocutaneus	984	Axilla	26–34
	B54	Axilla	39–48
n. medianus	B54	Axilla	0–1
	B57	Midarm	0–4
	984	Midforearm	0–1
	B58	Wrist	0–3
	B59	Wrist	0–1
n. ulnaris	B56 (R)	Midarm	palm: 0–1 dorsum: 55–56
	B58	Elbow	palm: 0–1 dorsum: 60–68
	B56 (L)	Midforearm	palm: 12–22 dorsum: 35–42
	997	Wrist	palm: 19–30 dorsum: 28–35
n. cutaneus antibrachii medialis	B58	Midarm	52–66
	B59	Midarm	51–57
n. intercosticobrachialis	B54	Axilla	45–52
n. cutaneus femoris lateralis	B57	Inguinal ligament	64–82
	B45	Inguinal ligament	51–69
n. femoris	B5	Inguinal ligament	56–63
	997	Inguinal ligament	47–52
n. saphenus	984	Knee	26–34
	B45	Knee	37–42
	997	Knee	17–28
n. cutaneus femoris posterior	B58	Upper buttock	52–66
n. ischiadicus	B59	Midthigh	51–57
	B56	Midthigh	57–64
n. peroneus communis	B57	Midthigh	9–15
	B58	Lower thigh	16–23
n. tibialis	B56	Lower thigh	toes: 0–8 dorsum: 36–43
	B54	Lower thigh	toes: 7–12 dorsum: 30–39

lowering in the central palmar area tends to separate the pattern into two principal portions: one located over the palmar surface of digits II, III and lateral half of IV and the other over the thumb and thenar

eminence (Fig. 8). These two portions of the pattern then continue to lower in resistance during the first 14 postoperative days until no area remains high except the tips of the thumb and digits II and III (B57, Fig. 8). The tips of these digits regain a normal resistance after about 50 days. When the palmar branch of the ulnar nerve is cut in

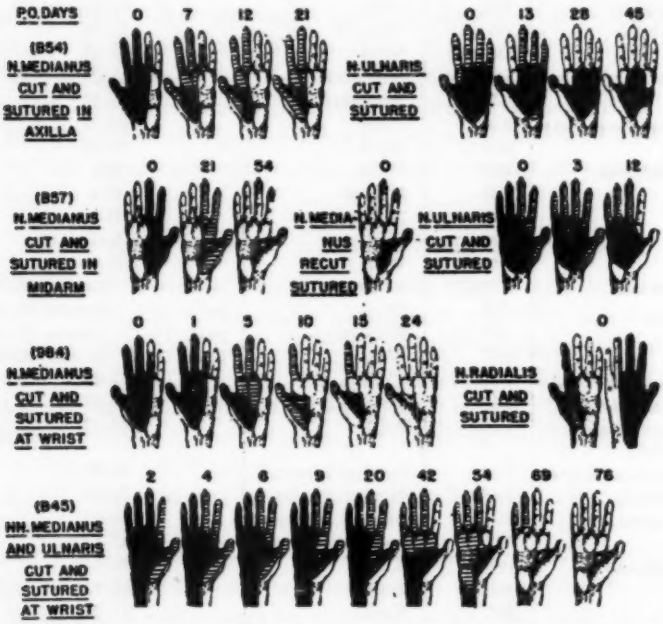
P.O. DAYS
0 7 12 21
(B54)
N. MEDIANUS CUT AND SUTURED IN AXILLA
N. ULNARIS CUT AND SUTURED
0 13 28 45
0 21 54
(B57)
N. MEDIANUS CUT AND SUTURED IN MIDARM
0
N. MEDIANUS RECUT SUTURED
N. ULNARIS CUT AND SUTURED
0 3 12
0 1 5 10 15 24
(B84)
N. MEDIANUS CUT AND SUTURED AT WRIST
N. RADIALIS CUT AND SUTURED
0
2 4 6 9 20 42 54 69 76
(B45)
NN. MEDIANUS AND ULNARIS CUT AND SUTURED AT WRIST

FIG. 8. Drawings summarizing changes in the skin resistance occurring in the palm following section and suture of *n. medianus*, *nn. medianus* and *ulnaris*, and *nn. medianus* and *radialis*. Solid black areas represent high skin resistance; cross-hatching indicates intermediate resistance.

an animal with a severed median nerve, the central median area and the palmar ulnar zone manifest a high resistance which remains high for 35 to 40 days before any lowering can be detected (B54, B57 in Fig. 8). When the ulnar nerve is sectioned alone these changes in the resistance of the central median zone are not found. If the radial nerve is cut in an animal with a previous median nerve section, the

thenar eminence and the volar surface of digits I, II, III, and lateral half of IV develop a high resistance along with the usual radial area on

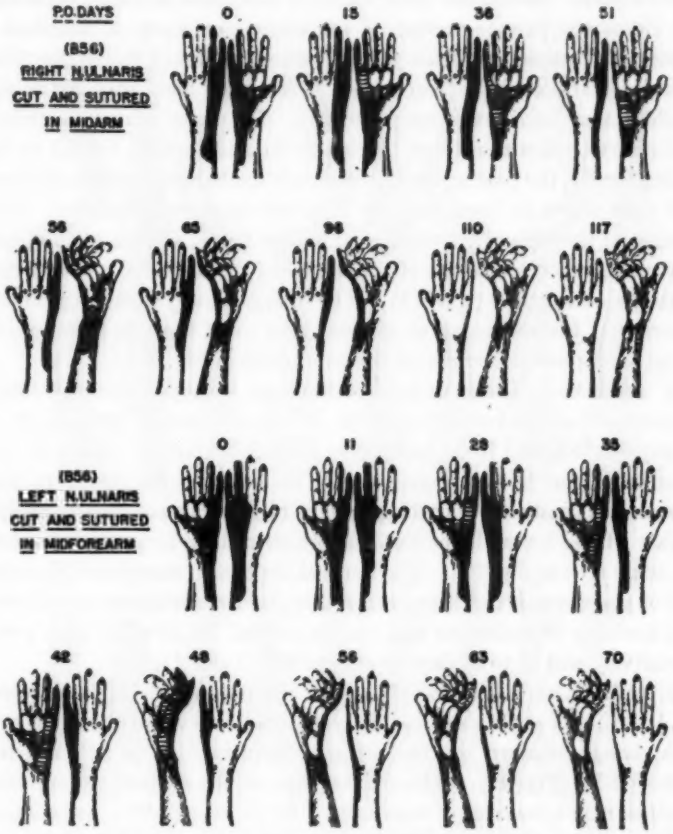

FIG. 9. Drawings summarizing postoperative alterations in the skin resistance pattern for *n. ulnaris* following section and suture. Solid black represents high resistance, cross-hatching intermediate resistance.

the dorsal surface of the hand (984 in Fig. 8). Thus sectioning of the median nerve in the rhesus monkey does not give a persistent pattern of high resistance over the median zone of the palm. It is necessary

to section the radial, palmar division of the ulnar, and the median nerve to obtain a persistent high resistance over the palm of the hand.

N. ulnaris. When the ulnar nerve is sectioned and sutured above the elbow the palmar portion of the ulnar area starts to manifest a lowering of resistance within 3 days postoperatively (Table 1). This lowering starts at the lateral border of the ulnar zone adjacent to the median area and progresses medially. In ulnar nerves sectioned and sutured below the elbow, i.e., below the anastomotic branch to the median nerve, the palmar high resistance is unchanged for 12 to 30 days and then starts to lower rapidly in a lateral-medial direction. The portion of the ulnar pattern located on the dorsal surface of the hand does not participate in the rapid changes just described as occurring on the palmar surface (Table 1). The zone gradually shrinks through a lowering of the resistance at its periphery until the last high area is found on the medial surface of the wrist (B56 in Fig. 9).

N. saphenus. The periphery of the zone of high resistance starts to lower on all its borders in 17 to 28 days in animal 997, in 26 to 34 days in 984, and in 37 to 42 days in B45 (Table 1). Since the regression of the pattern occurs at all its borders, the result of this process is a gradually shrinking area of high resistance on the medial surface of the leg with the last portion to change located just above the ankle (984 in Fig. 10). The femoral nerve area manifests this same sort of postoperative change except that the time relations are slower: first lowering of resistance was seen in animal B5 56 to 63 days postoperatively and 47 to 52 days in animal 997 (Table 1).

N. ischiadicus. The first change in the pattern of high resistance is a lowering of the resistance over the dorsal surface of the great toe. This change occurred by the 57th postoperative day in B59 and the 64th in B56 (Fig. 11). The plantar tips of the remaining four toes manifest next a lowering of resistance. By 81 days (B59) a recession of all the margins of the pattern on the leg and lower thigh is observed. At 113 days the resistance on the thigh is normal and only a narrow strip of high resistance remains on the lateral surface of the leg (B59 in Fig. 11). The dorsal surface of the foot shows a gradual recession of the pattern toward the lateral side of the foot. At 134 days (B59) the leg is normal except for a small area over the lateral malleolus and the foot shows continued shrinkage of the medial border of the pattern. The ulceration which appeared on the heel of B59 (photograph

24 in Fig. 6) during the third postoperative week started to heal when the resistance in this region began to lower. Similar ulcerations of the heel developed in B61 and B56 following transection of the sciatic

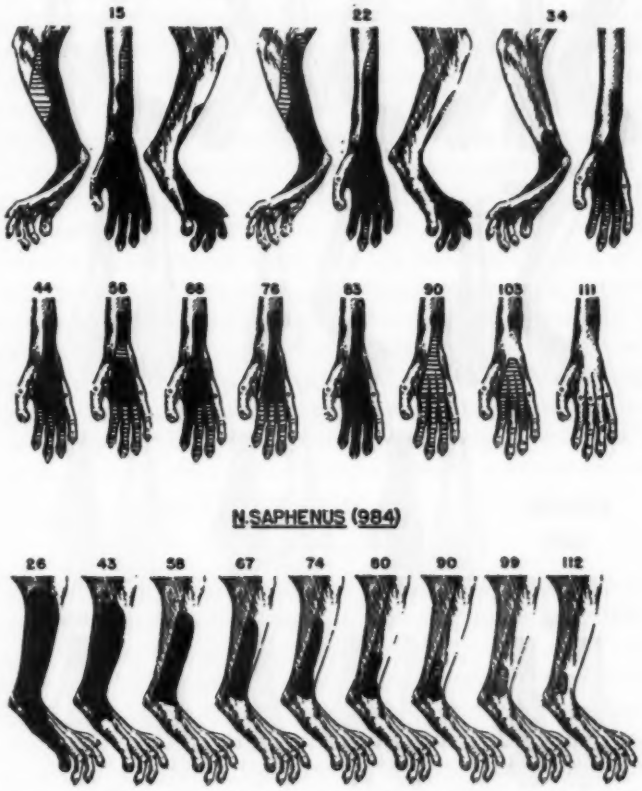

FIG. 10. Drawings summarizing postoperative alterations in skin resistance pattern for *n. peroneus communis* and *n. saphenus* following section and suture. Solid black represents high resistance, cross-hatching intermediate resistance. Numbers above the figures indicate the postoperative days.

nerve; in B61 the ulceration became infected and the animal had to be sacrificed and in B56 the ulceration began to heal when the skin resistance started to lower over the plantar surface of the foot.

N. peroneus communis. Large proximal portions of the leg pattern

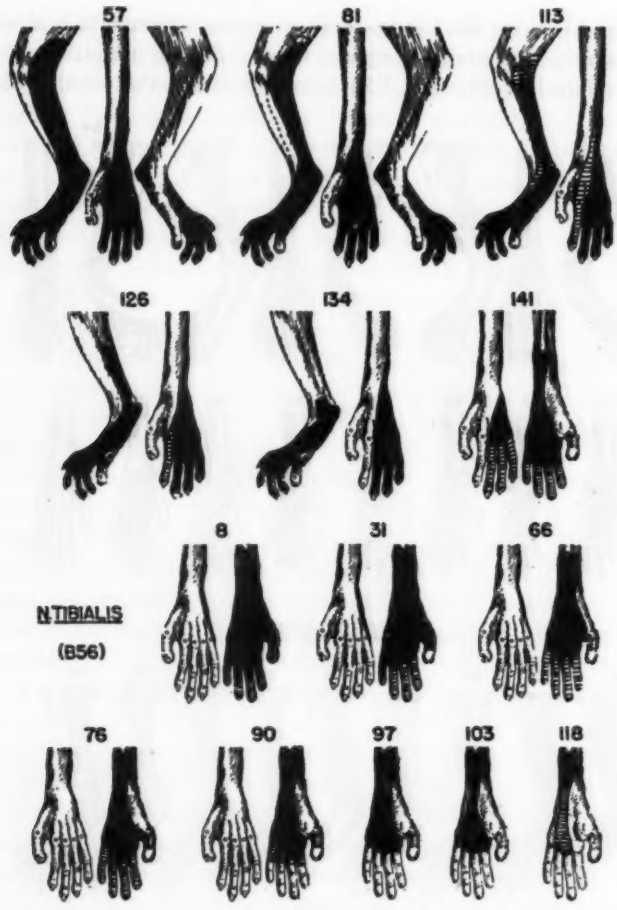

FIG. 11. Drawings summarizing postoperative alterations in skin resistance pattern for *n. ischiadicus* and *n. tibialis* following section and suture. Solid black represents high resistance, cross-hatching intermediate resistance. The numbers above the figures indicate the postoperative days.

begin to manifest a lowering of resistance about the 14th postoperative day (Fig. 10); this process progresses rapidly during the succeeding 20 days until all the leg pattern has returned to a normal resistance ex-

cept for a small zone over the lateral malleolus. A lowering of resistance over the dorsal surface of the toes and a regression of the medial border of the pattern starts around the 75th postoperative day (B57 in Fig. 10). In animal B57 this last spot of high resistance had nearly disappeared on the 111th postoperative day. On this 111th day B57 was reoperated: the common peroneal was exposed at the site of original suture, was retransected, and was resutured. Skin resistance examinations following this retransection show that the original area of high resistance is not restored completely by this procedure. The second pattern resembles most closely the original pattern around the 21st postoperative day when shrinkage of all thigh and leg borders had made appreciable progress.

N. tibialis. The plantar surfaces of the toes, starting first at the tips and progressing proximally, manifest a lowering of resistance within 12 days following tibial nerve transection and suture (Fig. 11). No further changes occur until about the 43rd postoperative day when the lateral strip over the ankle and dorsal surface of the foot begins to regress. The lateral-medial narrowing of the pattern continues and is soon accompanied by a distal-proximal shortening of the area on the plantar surface of the foot. The last area to regain a normal resistance is located over the heel (B56 in Fig. 11).

DISCUSSION

The areas of high skin resistance produced by peripheral nerve transections correspond closely to the regions supplied by the cutaneous branches of these nerves. Further, immediately after nerve section the patterns of high resistance, when applied to a type extremity, show no significant overlapping of borders. These areas of high resistance represent regions of anhydrosis and probably correspond to the zones of complete loss of sensation. Guttmann[2] described a comparable area using colorimetric methods. Skin resistance readings often reveal a zone of intermediate resistance surrounding the high area; this zone appears to represent a region of decreased sweat gland activity. These zones of intermediate resistance tend to have broad borders which gradually merge with adjacent normal regions; for this reason zones of intermediate resistance are difficult to demarcate and describe.

The borders of areas of high resistance resulting from peripheral nerve transection and suture do not remain static for any long interval

in the postoperative period. The postoperative alterations tend to occur at all peripheral borders, thereby producing the effect of an area shrinking gradually on all its borders until a central zone is the last to disappear. The chronology of these changes varies greatly from nerve to nerve. In general, the areas of high resistance on hands and feet, when produced by the transection and suture of a single nerve supplying these regions, manifest the most rapid regressions. If two nerves to the hand or the sciatic nerve to the foot be cut and sutured, then the speed of the lowering of resistance is slowed. It also appears that an area of high resistance produced on the forearm or leg by the transection and suture of a nerve to these regions tends to manifest a lowering of resistance more rapidly than an area similarly produced on the arm or thigh. Thus the data in this series of experiments suggest a tendency for a more rapid lowering of resistance in the distal portions of an extremity.

The chronology and location of skin resistance changes indicate that that not all the observations can be explained by regeneration of the severed sympathetic fibers. In addition to nerve regeneration, consideration must be given to neural overlapping and anastomosing, ingrowth of fibers from adjacent intact nerves, and artifactitious lowering of resistance by direct stimulation of sweat glands by heat or other agents (1, 2, 4, 8).

Neural overlapping and anastomosing supply the basis for explaining the rapid postoperative lowering of skin resistance on the palmar surface of the hand and plantar surface of the toes. The observations made on alterations in skin resistance following section of the median, ulnar, and radial nerves singly and in various combinations (summarized in Fig. 8) demonstrate that the ulnar and radial nerves overlap completely the median area of supply. The nerve fibers are distributed through small anastomotic branches observable in dissections of the hand. The experiments on sectioning the ulnar nerve at various levels in the arm and forearm demonstrate that the median nerve supplies some sympathetic fibers to the ulnar area on the palm and that these fibers reach the ulnar nerve through the anastomotic branch constantly present at the elbow in the rhesus monkey.

The possibility of ingrowth of sympathetic fibers from adjacent normal nerves must be given consideration in seeking to explain the

lowering of resistance which starts about the periphery of an area of high resistance during the early postoperative weeks. There are at least two reasons for doubting that this peripheral lowering of resistance is due to regeneration of sympathetic fibers through the severed nerve: 1) the process can be detected in some areas too early for nerve regeneration, and 2) the lowering tends to involve distal as well as proximal borders. Weddell, Guttmann and Gutmann (14) have shown that, after isolated section of the sural nerve in the rabbit, there is a shrinkage in the area of sensory loss due to an ingrowth of nerve fibers from surrounding normal nerves. They have demonstrated that similar local extensions of nerve fibers occur following section of the tibial and peroneal nerves. These shrinkages in denervated areas commence in some cases as early as the day following transection and are clearly apparent 18 to 26 days postoperatively, according to the data recorded by these workers. Further, the correspondence between the boundary obtained physiologically and that seen histologically shows that an actual extension of nerve fibers into the denervated area takes place. Further studies are necessary before any conclusions can be reached concerning the occurrence of such a fiber ingrowth into sympathectomized areas of skin.

Artifacts in skin resistance borders due to direct stimulation of denervated sweat glands by local heat, parasympatheticomimetic drugs, or other agents, must be given consideration in interpreting results of skin resistance studies. Gurney and Bunnell (1) have shown that local heat can stimulate denervated sweat glands in the human. There is reason to believe that this observation holds also for sweat glands in the rhesus monkey. Hence the application of heat must be controlled lest excessive rises in local temperature stimulate denervated sweat glands and produce erroneous borders. Since the experiments of Langley (6, 7) it has been known that pilocarpine produces activity in denervated sweat glands through direct stimulation. This precludes the use of pilocarpine as a method of inducing sweating for skin resistance studies. Furmethide has been recommended as the sudorific agent for skin resistance studies (3, 5). The stimulation of denervated sweat glands by Furmethide noted in these experiments on rhesus monkeys indicates the need for further evaluation of Furmethide as a sudorific.

The final stages of shrinkage of the skin resistance patterns and

the eventual disappearance of the area of high resistance are interpreted as being due to regeneration of the severed sudorific fibers. The period required for this disappearance of the skin resistance pattern varies from 3 to 6 months, depending upon the nerve and level of section. Further studies by the skin resistance method combined with histological analyses of the disturbed nerve trunks and denervated areas of skin are being carried out with the aim of obtaining additional information concerning the rates and conditions of regeneration of sudorific nerve fibers.

SUMMARY

1. Disturbances in sweat secretion in rhesus monkeys following transection of a peripheral nerve cause an elevation of the resistance of the skin to the passage of an electric current. The borders of such an area of altered conductivity show a general correspondence to the region of cutaneous supply of the severed nerve.

2. The elevation of resistance varies from being sufficiently high to cause almost no flow of current in the circuit to a state where the amount of flow is only slightly less than in normally innervated skin. The areas of high skin resistance, determined by marking the site of first flow of direct current through the circuit, generally correspond to the anatomical area of autonomous supply described by others using different techniques. Functionally, this is the area of anesthesia and anhydrosis. Areas of intermediate resistance, which surround an area of high resistance, correspond to the mixed or intermediate zone of a peripheral nerve. This zone represents anatomically the portion of skin supplied by both the transected nerve and intact nerves adjacent to it; functionally, it is the region of hypesthesia and hypohydrosis. Intermediate resistance areas have no sharp borders as is the case of regions of high resistance.

3. The borders of areas of elevated skin resistance are static for only short periods of time. Immediately following section of a peripheral nerve, the area of high resistance is maximal. Soon, often 24 hours or less postoperatively, there may be detected a lowering of resistance at the periphery of the area of high resistance. This initial lowering is seen most prominently after section of a nerve supplying the palm or sole and is interpreted as being due to neural overlapping. The

area of high resistance which remains after this initial lowering of resistance about its periphery thus represents the autonomous zone of the blocked nerve. In many nerves, particularly those supplying more distal portions of the extremities, a further lowering of resistance about the periphery of the area of high resistance becomes prominent at 14 to 21 postoperative days. The possibility of this lowering being due to ingrowth of sudorific fibers from adjacent intact nerves is suggested by the chronology and symmetrically peripheral location of the change.

4. A slow shrinkage of the borders of the remaining pattern of high resistance occurs over a period of 3 to 6 months, depending upon the nerve and the level of transection and suture. This process results in the disappearance of the region of elevated skin resistance. This final slow shrinkage is interpreted as a functional manifestation of regeneration of the sudorific nerve fibers through the sectioned nerve.

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BOOK REVIEWS

The Chemistry of Anaesthesia. By JOHN ADRIANI. 502 pp. Illus. $7.00. *Charles C Thomas, Springfield, Illinois,* 1945.

This welcome volume, intended primarily for the anesthetist, gathers together a large mass of interesting information from a great many scattered sources. All anesthetists are indebted to Dr. Adriani for his diligence in providing them with a very convenient reference book, the first such book on the chemistry of anesthesia.

The subject is logically divided into sections on organic chemistry, inorganic chemistry, and biochemistry. The first section contains in addition an exposition of the gas laws and their application to the administration of anesthesia, and an account of the carbon dioxide absorption method and of various other technical matters the importance of which is so often neglected by anesthetists.

The material is presented in such a clear and simple manner that none of the various groups interested in anesthesia should have any difficulty in understanding the text. The typography and illustrations are excellently done. There is a good bibliography.

Useful as this book will be to the anesthetist on his daily rounds, it may serve a greater purpose. By bringing together most of the available information on the subject, it makes quite evident how little we really do know about the relation of chemistry and especially of biochemistry to anesthesia, and how much work remains to be done.

M. H. H.

Penicillin in the Treatment of Infections. By CHESTER S. KEEFER and DONALD G. ANDERSON. 249 pp. $1.50. *Oxford University, New York, New York,* 1945.

This is an authoritative, well arranged review of the whole subject of penicillin therapy in which the important contributions are discussed critically and concisely. The authors have had a wide experience in the clinical use of penicillin; in this report they have included much of their own data, and have made generous use of clinical charts to illustrate the influence of penicillin on various typical infections. In the opinion of the reviewer they have managed very well to concentrate a great deal of information in relatively few pages without making their opinions seem too didactic or final.

A. M. F.

VD Manual for Teachers. By SAMUEL D. ALLISON and JUNE JOHNSON. 149 pp. $2.00. *Emerson Books, Incorporated, New York, New York,* 1946.

This book is exactly what its title says that it is; a "VD Manual for Teachers" (of secondary schools). It is divided into three sections. The first of these opens by stating the case for VD education of youth before infection occurs. It then

presents a perhaps too brief outline of what is (and is not) being done about it in the schools of the United States and Canada. It is unfortunate that reference is nowhere made to more extensive studies of school VD and sex education programs. The section concludes with a plan under which the teaching program may be developed. It is maintained, wisely, that VD education should be a function of health education and not of sex education; that the teachers, themselves, should do the teaching rather than to leave it to visiting specialists, and that the subject may be taught in almost any department, from Chemistry to English. Good examples are offered as to how this may be done.

The second section gives the teacher a foundation of information about the several venereal diseases, in simple language, and closes with a four page list of reference material, largely of the popular, non-technical variety. The only serious error noted was the implication, on page 57, and the statement, on page 63, that syphilis produces almost no immunity to reinfection. This is essentially true only of infections which have been biologically cured during the very early stages.

The third, and last, section describes, and discusses the use of teaching aids, and indicates where they may be obtained.

This book should be a very welcome help to teachers in a field which has been neglected much too long in far too many places.

N. A. N.

In the Doctor's Office. By ESTHER JANE PARSONS. 295 pp. $2.00. Published by *J. B. Lippincott Co., Philadelphia, Pennsylvania*, 1945.

Drawing from her wide experience as a medical assistant and teacher, Miss Parsons has prepared a practical guide for those who assist the doctor; whether in a small practice where the duties of receptionist, secretary, nurse and technician are combined in one person, or in a large office where persons trained in each of these fields is employed.

The early part of the book deals with the essential attributes (appearance, personality, poise, tact, etc.) of a person to be selected as a medical assistant. The person thus carefully selected is drilled in medical ethics, legal considerations, meeting the public, and obtaining information from the patients.

In the remaining chapters the medical assistant is given advice and suggestions in laboratory technique, care of office equipment, sterilization fundamentals, use of the telephone, medical book-keeping, handling correspondence, filing, literary research, and preparing medical manuscripts.

The book in a concise and simple manner thoroughly answers the question "How can I best serve the doctor and his patient?"

There is a bibliography of 20 titles and an adequate index. The text is enlivened by amusing drawings by Jean McConnell.

B. F. P.

A Textbook of Surgery by American Authors. 4th Ed. By FREDERICK CHRISTOPHER. 1548 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1945.

This completely revised edition of Christopher's textbook of surgery is a veritable encyclopedia of surgical information. The individual sections are written by 201 leading American authorities. This edition has two columns to a page with an average of about 800 words to a page, or over 1,200,000 words for the entire book. The number of pages is less than in the second edition, but the number of words and of illustrations has been increased.

In any work of this type, which in a way is a one-volume system of surgery, rather than a textbook written by a single author, three conditions must be met to establish excellence in the product. First, the individual authors must be pre-eminent in their fields, and must be able to express themselves clearly in writing. Second, the accounts in the particular book under consideration must represent a worthy effort by these experts and not be an abbreviated and hastily put together revision of their older works on the subject. Third, the chapters must be strictly up-to-date. It is impossible in any work of this sort to fulfill all three of these standards in all instances. However, in this particular book these ideals are lived up to very well indeed. The matter of the choice of authors deserves mention. These men are chosen from all parts of the country and the following list of a few of them includes names of those who are either undisputed leaders in their field, or who share this position of leadership with others. Such names include: Alexander—atelectasis; Blalock—shock; Bunnell—tendons; Cattell—ulcerative colitis; Coller—water balance; David—polypoid tumors of the large bowel; Donovan—congenital malformations of the stomach; Harrington—diaphragmatic hernia; Heuer—tumors of the mediastinum; Holman—aneurysms; Ivy—facial fractures; Ladd—anomalies of the small intestine; Martin—cancer of the lip; Meleney—surgical bacteriology; Pool—surgery of the spleen; Rankin—carcinoma of the colon; and Wangensteen—intestinal obstruction. In general these men have extended themselves and given of their best, and on the whole the accounts are strictly up-to-date. For example, the sections on military surgery by Churchill, and on chemotherapy and surgical infections by Lockwood, are new presentations written especially for this edition. Many new sections have been added or have been entirely rewritten by new authors for this edition.

A great deal of surgical information is compressed into this single volume textbook of surgery. Dr. Christopher has done an excellent job of correlating and assembling the writings of many leaders in surgery into a single coherent book. It can be recommended to medical students and practitioners and affords a handy one-volume modern reference book for all those interested in surgery.

H. N. H.

The Treatment of Peptic Ulcer. By GEORGE J. HEUER, assisted by CRANSTON HOLMAN and WILLIAM A. COOPER. $3.00. 118 pages. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1944.

This book is an excellent example of one particular type of clinical research. The case histories of 1139 patients with peptic ulcer seen during a ten year period at the New York Hospital have been thoroughly studied. The thoroughness of

this study is worthy of commendation and the conclusions drawn from this study by Dr. Heuer are worthy of recognition.

Interesting observations include the following:—The direct mortality from ulcer treated medically in the New York series is 3.5%, a mortality which, in the authors' experience approaches closely that of gastro-enterostomy and gastric resection. Medical management of cases with severe bleeding gives too high a mortality if routinely carried out. The authors are inclined toward surgery in carefully selected cases. Question of malignancy and its relation to gastric ulcer receives careful attention in this book. The authors state that "All cases in which the results of the diagnostic methods are equivocal at first examination, and particularly those in which the gastric acidity as determined by the method described is low or absent, should be considered as candidates for surgery." The results of gastro-enterostomy and gastric resection are compared and the advantages accruing to each of these procedures are presented. In various papers the results following the classical simple closure of a perforated duodenal ulcer varied tremendously. In Heuer's series only slightly over 50% of the patients had satisfactory results. The relation of gastro-enterostomy and of gastric resection to the acid secretion of the stomach represented an important part of this monograph. These studies throw considerable light on the question of whether or not to do a radical or a conservative gastric resection. This book deserves study by all those interested in surgery of the stomach.

H. N. H.

An Introduction to Physical Anthropology. By M. F. Ashley Montagu. 326 pp. $4.00. *Charles C Thomas, Springfield, Ill.*, 1945.

The author, an anatomist, attempts in this little book to provide and interpret the essential facts which have become available from "the comparative science of man as a physical organism in relation to his total environment, social as well as physical." The paramount problem of physical anthropology the author sees in the question "What are the causes which produced, and which continue to produce, man in all his infinite variety?"

The opening, brief and elementary chapter deals with the scope and definition of physical anthropology. The following two chapters describe the many different forms of primates and discuss their evolution. This section contains a great many erroneous and doubtful statements, omits much of significance, and includes information on behavior which has no real bearing on physical anthropology. This *Introduction* gives most inadequate space to the large and highly important subject of physical growth and development in human groups, but finds room for much irrelevant information, such as: "The gorilla builds himself a comfortable nest which he uses once only, and abandons in the morning."

The fourth chapter, on the origin and evolution of man, is mainly an enumeration of the more significant fossil remains of man, followed by a discussion of their interrelations. Since the book is intended not only for the general reader, but also for biologists and physicians, one could expect a somewhat more technical treat-

ment of these important discoveries, especially some metric data besides the overrated absolute size of the cranial capacity. One also misses here a more than superficial presentation of man's evolutionary specializations.

The fifth and sixth chapters deal with the main divisions and "ethnic groups" of recent man. Here Dr. Montagu tries to belittle the work of "race classifiers" and of the "older school" of physical anthropologists, but uses the results of their work almost exclusively. The few new claims of what is supposedly the "newer school" are not very convincing. For instance, why should sacral spots in infants of Bushman and Hottentots "strongly suggest" a Mongoloid admixture, if the same spots are also common in negroes and whites? Few anthropologists will take kindly to the assertion that some early immigrants to the New World, forming the American Indians, have been "dominantly Caucasoid with some Mongoloid admixture" or, as stated in the fourth chapter, "were almost certainly of Caucasloid type."

The seventh chapter has very little justification in this introduction to physical anthropology. It is entitled "The Relation between Body, Mind, and Culture" and represents a somewhat forced mixture of biological facts with speculations regarding spiritual and cultural qualities. To quote just one typical sentence: "The genes provide the necessary factors for the development of a brain and a nervous system, but the potentialities of that brain and nervous system can never be realized in the absence of the human social stimuli which serve to organize those tissues into a human mind." Incidentally, it seems strange to find an anatomist speaking of "brain *and* nervous system" and of the "lower leg", to discover in an earlier chapter that "tracts from *all* the senses" go to the neopallium, and to read of a "rhinopallium" which probably stands for either archipallium or rhinencephalon.

The eighth chapter, entitled "Heredity and the Influence of the Environment upon Man", is an uncritical and incomplete attempt to summarize the more or less tentative results of the vast and comparatively young field of human biology.

From the appendix, devoted to a "practical synopsis of methods of measurement in physical anthropology", it is apparent that the author is not an experienced physical anthropologist and has not mastered the essentials of the technique which is the efficient servant of the science he has aimed to introduce.

As an outline of a large and specialized field of knowledge, intended for outsiders, this work is not properly balanced, too incomplete and not sufficiently reliable to be recommended, but as a collection of Dr. Montagu's thoughts and interpretations of many aspects of physical anthropology the book is not without interest to experts.

A. H. S.